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(54) Title: **PIPERAZINE DERIVATIVES AND PROCESS FOR THE PREPARATION THEREOF**

(57) Abstract

The present invention relates to novel compound having strong antitumor activities of general formula (I), wherein R₁ and R₂ are independently hydrogen, substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₃-C₆ cycloalkyl, substituted or unsubstituted C₂-C₈ unsaturated alkyl, ketone, substituted or unsubstituted aryl, substituted or unsubstituted C₁-C₄ alkoxy, substituted or unsubstituted arylhydroxy, substituted or unsubstituted amino, C₁-C₄ lower ester, C₁-C₄ lower thioester, thiol, substituted or unsubstituted carboxyl, epoxy, substituted or unsubstituted C₁-C₄ lower thioalkoxy; or R₁ and R₂ are fused to form C₃-C₄ saturated or unsaturated chain; R₃, R₄, R₅, R₆ and R₇ are independently hydrogen, halogen, hydroxy, nitro, C₁-C₄ lower ester, C₁-C₄ lower alkyl, C₁-C₄ lower thioalkyl, substituted or unsubstituted C₃-C₆ cycloalkyl, C₁-C₄ lower alkoxy, C₁-C₄ lower thioalkoxy, substituted or unsubstituted aryl, substituted or unsubstituted lower arylalkoxy, substituted or unsubstituted lower alkylamino, or lower alkyl substituted or unsubstituted carbamate; or among R₃, R₄, R₅, R₆ and R₇, two adjacent groups are bonded with each other to form 1,2-phenylene or 2,3-naphthylene; X is oxygen, sulfur, or substituted or unsubstituted imino; Y is bonded at the 3-position or 4-position of the aromatic ring part wherein Y is oxygen or -NR₈- (wherein, R₈ is the same with the above-mentioned R₃); Z is hydroxy, C₁-C₄ lower alkoxy, C₁-C₄ lower thioalkoxy, substituted or unsubstituted aryloxy, C₁-C₄ lower alkylamino, substituted or unsubstituted cycloamino containing 1-5 nitrogen atoms; A is nitrogen or -CH-; its pharmaceutically acceptable acid addition salts and process for the preparation thereof.

(I)

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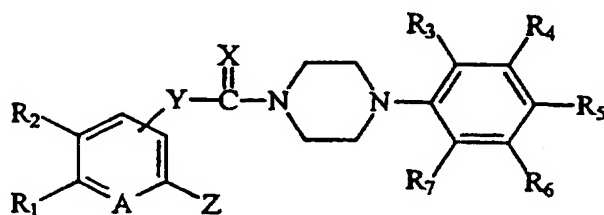
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Piperazine derivatives and process for the preparation thereof

The present invention relates to new piperazine derivatives of the general formula (I)

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(I)

wherein R₁ and R₂ are independently hydrogen, substituted or
 15 unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₃-C₆ cycloalkyl,
 substituted or unsubstituted C₂-C₈ unsaturated alkyl, ketone, substituted
 or unsubstituted aryl, substituted or unsubstituted C₁-C₄ alkoxy,
 substituted or unsubstituted arylhydroxy, substituted or unsubstituted
 amino, C₁-C₄ lower ester, C₁-C₄ lower thioester, thiol, substituted or
 20 unsubstituted carboxyl, epoxy, substituted or unsubstituted C₁-C₄ lower
 thioalkoxy; or R₁ and R₂ are fused to form C₃-C₄ saturated or
 unsaturated chain; R₃, R₄, R₅, R₆ and R₇ are independently hydrogen,
 halogen, hydroxy, nitro, C₁-C₄ lower ester, C₁-C₄ lower alkyl, C₁-C₄
 lower thioalkyl, substituted or unsubstituted C₃-C₆ cycloalkyl, C₁-C₄
 25 lower alkoxy, C₁-C₄ lower thioalkoxy, substituted or unsubstituted aryl,
 substituted or unsubstituted lower arylalkoxy, substituted or
 unsubstituted lower alkylamino, or lower alkyl substituted or
 unsubstituted carbamate; or among R₃, R₄, R₅, R₆ and R₇, two adjacent
 groups are bonded with each other to form 1,2-phenylene or
 30 2,3-naphthylene; X is oxygen, sulfur, or substituted or unsubstituted
 imino; Y is bonded at the 3-position or 4-position of the aromatic ring
 part wherein Y is oxygen or -NR₈- (wherein, R₈ is the same with the
 above-mentioned R₃); Z is hydroxy, C₁-C₄ lower alkoxy, C₁-C₄ lower
 thioalkoxy, substituted or unsubstituted aryloxy, C₁-C₄ lower alkylamino,
 35 substituted or unsubstituted cycloamino containing 1-5 nitrogen atoms;
 A is nitrogen or -CH=; its pharmaceutically acceptable acid addition

salts and process for the preparation thereof.

In the above definitions, C₁-C₈ alkyl means straight or branched alkyl group such as methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, 5 tert-butyl, pentyl, iso-pentyl, hexyl, heptyl, octyl, 2-methylpentyl or the like.

C₁-C₄ lower alkyl means methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl or tert-butyl.

Substituted or unsubstituted C₃-C₆ cycloalkyl means substituted or 10 unsubstituted cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, substituted cyclopropyl, substituted cyclopentyl, substituted cyclohexyl or the like.

C₁-C₄ lower ester means a carboxyl group esterified by a lower alkyl group.

15 C₁-C₄ lower alkoxy means methoxy, ethoxy, propoxy, isopropoxy, butyloxy, isobutyloxy, tert-butyloxy group or the like.

C₁-C₄ lower thioalkoxy means methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, tert-butylthio group or the like.

C₁-C₄ lower alkylamino means methylamino, ethylamino, propylamino, 20 butylamino group or the like.

Aryloxy means phenoxy, substituted phenoxy, naphthyloxy or substituted naphthyloxy or the like.

Cycloamino group containing 1-5 nitrogen atoms means pyrrolidinyl, pyrrolinyl, imidazolyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, 25 triazolyl, tetrazolyl, piperazinyl or the like.

The present inventors had studied for a long time to find compounds having intensive antitumor activity. As the results, now we have finally found out the facts that the present compounds of the general 30 formula(I) and acid addition salts thereof have not only prominent antitumor activities but very low toxicities.

Accordingly, the one object of the present invention is to provide the novel compounds of the general formula(I) and acid addition salts thereof having not only prominent antitumor activities but very low 35 toxicities.

The other object of the present invention is to provide a process for

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the preparation of the compounds of general formula(I) and acid addition salts thereof.

The compounds of the present invention can be mixed with pharmaceutically acceptable vehicles by a known method to give
5 pharmaceutical compositions and the pharmaceutical compositions can be used to prevent or treat with various kinds of tumors of human beings or mammals.

Therefore, another object of the present invention is to provide pharmaceutical compositions containing the compounds of the general
10 formula(I) or acid addition salts thereof as active ingredients.

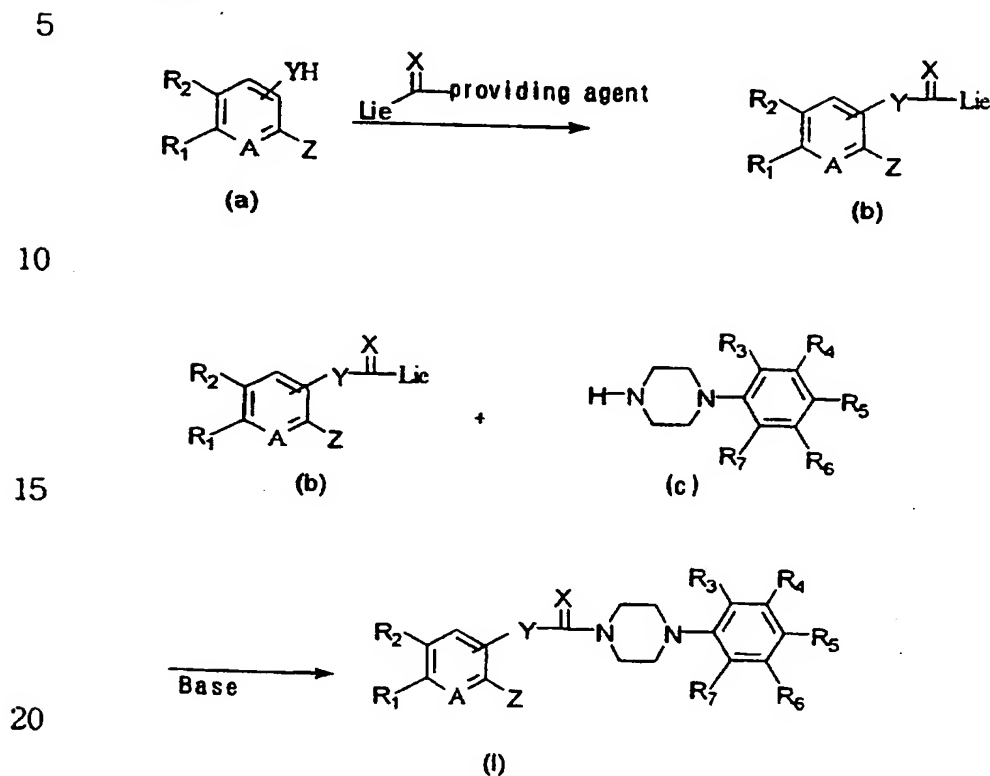
Acids which can be reacted with the compounds of the general formula(I) to form acid addition salts are pharmaceutically acceptable inorganic or organic acids; for example, inorganic acids such as hydrochloric acid, bromic acid, sulfuric acid, phosphoric acid, nitric acid;
15 organic acids such as formic acid, acetic acid, propionic acid, succinic acid, citric acid, maleic acid, malonic acid, glycolic acid, lactic acid; amino acids such as glycine, alanine, valine, leucine, isoleucine, serine, cysteine, cystine, asparaginic acid, glutamic acid, lysine, arginine, tyrosine, proline; sulfonic acids such as methane sulfonic acid, ethane
20 sulfonic acid, benzene sulfonic acid, toluene sulfonic acid; or the like.

Vehicles which can be used in the preparation of pharmaceutical compositions containing the compounds of the general formula(I) as active ingredients are sweetening agent, binding agent, dissolving agent, aids for dissolution, wetting agent, emulsifying agent, isotonic agent,
25 adsorbent, degrading agent, antioxidant, antiseptics, lubricating agent, filler, perfume or the like; such as lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, glycine, silica, talc, stearic acid, stearin, magnesium stearate, calcium stearate, magnesium aluminum silicate, starch, gelatine, tragacanth gum, glycine, silica, alginic acid, sodium alginate, methyl
30 cellulose, sodium carboxy methyl cellulose, agar, water, ethanol, polyethylenglycol, polyvinyl pyrrolidone, sodium chloride, potassium chloride, orange essence, strawberry essence, vanilla aroma or the like.

Daily dosage of the compound of the general formula(I) may be varied depending on age, sex of patient and the degree of disease. Daily
35 dosage is 1.0mg to 5,000mg may be administered one to several times.

The compounds of the general formula (I) according to the present invention may be prepared by the following scheme 1.

Scheme 1



wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , A, X, Y and Z are as defined above, and Lie is a leaving group such as halogen atom, sulfonyl or the like.

25

The above process comprises reacting a compound of the general formula(a) with a $-\text{C}(=\text{X})-$ group-providing agent in organic solvent to obtain a compound of the general formula(b) and successively reacting the compound of the general formula(b) with a compound of the general formula(c) to give the compound of the general formula(I). The used $-\text{C}(=\text{X})-$ group-providing agent preferably be selected from 1,1-carbonyldiimidazole, 1,1-carbonylthiodiimidazole, phosgene, thiophosgene, carbonyldiphenoxide, phenylchloroformate or the like.

30

35

The reaction may be carried out in conventional organic solvent such as, for example, tetrahydrofuran, dichloromethane, chloroform,

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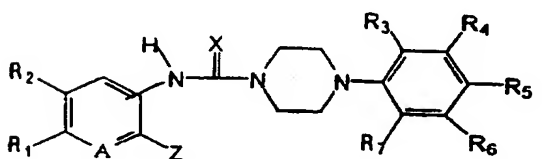
acetonitrile.

And also the reaction is preferably carried out in the presence of coupling agent such as conventional inorganic or organic base. Such conventional inorganic or organic base used in the reaction means

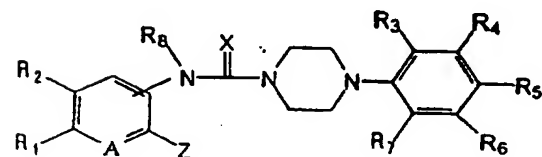
- 5 sodium hydride, potassium hydride, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium bicarbonate, potassium bicarbonate, triethylamine, pyridine, DBU or the like, and 1-1.5 equivalent, preferably 1-1.1 equivalent thereof may be used.
- 10 The reaction may be carried out between 3°C and boiling point of the solvent used, preferably at 50°C-100°C for 5 - 48 hours, preferably for 10 - 24 hours.
- C(=X)-group-providing agent may be used in an amount of 1 - 1.5 equivalent, preferably 1-1.1 equivalent to the starting compound.

15 A compound of the general formula(I) wherein Y is -NR₈- may be prepared by the following scheme II

Scheme II.



(Ia)



(Ib)

wherein, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, A, X and Z are as defined above.

A compound of the general formula(Ib) above may be prepared effectively by introducing R₈ providing agent into a compound of the
5 general formula(Ia).

R₈ providing agent preferably used in the above reaction is C₁-C₈ lower alkylhalogen, C₁-C₈ lower alkyl sulfonate, substituted or unsubstituted C₃-C₈ cycloalkylhalogen, arylhalogen, substituted or unsubstituted C₃-C₈
10 cycloalkyl sulfonate, arylsulfonate, or the like.

C₁-C₈ lower alkylhalogen means methylchloride, methylbromide, methyliodide, ethylchloride, ethylbromide, ethyliodide, propylchloride, propylbromide, propyliodide, butylchloride, butylbromide, butyliodide,
15 pentylchloride, pentylbromide, pentyliodide, ethylbromoacetate, or the like.

C₁-C₈ lower alkyl sulfonate means methylsulfonate, ethylsulfonate, propylsulfonate, butylsulfonate, pentylsulfonate, or the like.

20 Substituted or unsubstituted C₃-C₈ cycloalkylhalogen cyclopropylchloride, cyclopropylbromide, cyclopropyliodide, cyclobutylchloride, cyclobutylbromide, cyclobutyliodide, cyclopentylchloride, cyclopentylbromide, cyclopentyliodide, cyclohexylchloride, cyclohexylbromide, cyclohexyliodide, cyclopropyl methylchloride,
25 cyclopropyl methylbromide, cyclopropyl methyliodide, cyclobutyl methylchloride, cyclobutyl methylbromide, cyclobutyl methyliodide, cyclopentyl methylchloride, cyclopentyl methylbromide, cyclopentyl methyliodide, cyclohexyl methylchloride, cyclohexyl methylbromide, cyclohexyl methyliodide, or the like.

30 Arylhalogen means benzylchloride, benzylbromide, benzyliodide, benzoylchloride, benzoylbromide, benzoyliodide, toluylchloride, toluylbromide, toluyliodide, or the like.

35 Substituted or unsubstituted C₃-C₈ cycloalkyl sulfonate means cyclopropyl sulfonate, cyclobutyl sulfonate, cyclopentyl sulfonate,

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cyclohexyl sulfonate, methylcyclopropyl sulfonate, methylcyclobutyl sulfonate, methylcyclopentyl sulfonate, methylcyclohexyl sulfonate, or the like.

- 5 Arylsulfonate means benzyl sulfonate, benzoyl sulfonate, toluyl sulfonate, or the like.

More particularly, a compound of the general formula (1a) may be reacted with an alkylating agent or arylating agent in a solvent at the
10 temperature of 25-80°C, for 30 minutes - 20 hours to give the object compound of the general formula(Ib).

An alkylating agent or arylating agent may be used in amount of 1.0 - 1.5 equivalent.

Conventional organic solvent such as for example tetrahydrofuran,
15 dichloromethane, acetonitrile, dimethylformamide may be used in the above reaction.

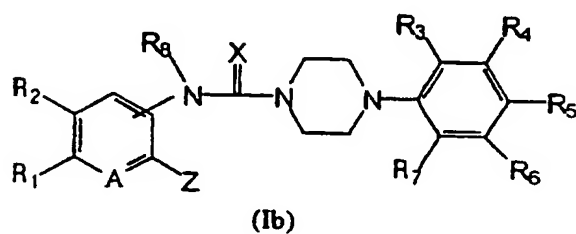
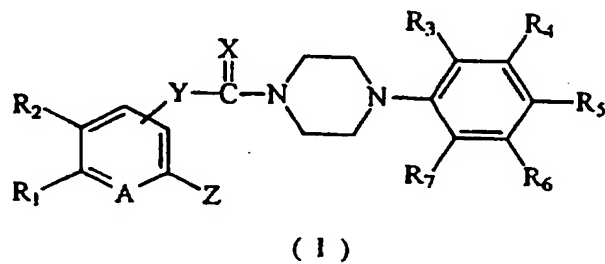
In the above reactions, if any acid material is formed, any basic material may be preferably added as scavenger in order to eliminate the
20 acid material from the reaction phase. Such basic material may be alkali metal hydroxide, alkali earth metal hydroxide, alkali metal oxide, alkali earth metal oxide, alkali metal carbonate, alkali earth metal carbonate, alkali metal hydrogen carbonate, alkali earth metal hydrogen
25 carbonate such as sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, magnesium oxide, calcium oxide, potassium carbonate, sodium carbonate, calcium carbonate, magnesium carbonate, magnesium bicarbonate, sodium bicarbonate, calcium
bicarbonate or the like, or organic amines.

- 30 The compound of the general formula(a) is described in prior art (J. Med. Chem., 1992; 35, 3784, 3792) or may be prepared in a similar method to the art.

- 35 Hereinafter the present invention will be described in more details with reference to following examples but it is not intended to limit the scope

of the invention thereinto.

Compounds of the general formula(I) and formula(Ib) are prepared in following examples according to the above-mentioned process.







20 wherein R₁, R₂, R₃, R₄, R₅, R₆, R₇, A, X, Y, Z are the same above.
















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












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


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

| Ex. No. | R ₁ | R ₂ | R ₃ | R ₄ | R ₅ | R ₆ | R ₇ | A | X | Y | Z | Y |
|------------|----------------|----------------|---|----------------|----------------|----------------|----------------|---|---|----|-----|-----|
| 1 | Me | Me | SMe | H | H | H | H | N | O | NH | OMe | 3-N |
| 2 | Me | Me |  | H | H | H | H | N | O | NH | OMe | 3-N |
| 3 | Me | Me | Me | Me | H | Me | Me | N | O | NH | OMe | 3-N |
| 4 | Me | Et | SMe | H | H | H | H | N | O | NH | OMe | 3-N |
| 5 | Me | Et |  | H | H | H | H | N | O | NH | OMe | 3-N |
| 6 | Me | Et | Me | Me | H | Me | Me | N | O | NH | OMe | 3-N |
| 7 | Me | Et | H | SH | H | H | H | N | O | NH | OMe | 3-N |
| 8 | Me | nPr | H | OMe | H | OMe | H | N | O | NH | OMe | 3-N |
| 9 | Me | nPr | H | Me | H | Me | H | N | O | NH | OMe | 3-N |
| 10 | Me | nPr | H | F | H | F | H | N | O | NH | OMe | 3-N |
| 11 | Me | nPr | OMe | H | H | H | H | N | O | NH | OMe | 3-N |
| 12 | Et | Me | H | OMe | H | OMe | H | N | O | NH | OMe | 3-N |
| 13 | Et | Me | H | Me | H | Me | H | N | O | NH | OMe | 3-N |
| 14 | Et | Me | H | OH | H | H | H | N | O | NH | OMe | 3-N |

| Ex. No. | R ₁ | R ₂ | R ₃ | R ₄ | R ₅ | R ₆ | R ₇ | A | X | Y | Z | Y |
|---------|------------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|---|---|----|---|-----|
| 15 | nPr | Me | H | OMe | H | OMe | H | N | O | NH | OMe | 3-N |
| 16 | nPr | Me | H | Me | H | Me | H | N | O | NH | OMe | 3-N |
| 17 | nPr | Me | H | OH | H | H | H | N | O | NH | OMe | 3-N |
| 18 | -(CH ₂) ₃ - | | H | OMe | H | OMe | H | N | O | NH | OMe | 3-N |
| 19 | -(CH ₂) ₃ - | | H | Me | H | Me | H | N | O | NH | OMe | 3-N |
| 20 | -(CH ₂) ₄ - | | H | OMe | H | OMe | H | N | O | NH | OMe | 3-N |
| 21 | -(CH ₂) ₄ - | | H | Me | H | Me | H | N | O | NH | OMe | 3-N |
| 22 | Me | Me | H | Me | H | Me | H | N | S | NH | OMe | 3-N |
| 23 | Me | Me | H | F | H | F | H | N | S | NH | OMe | 3-N |
| 24 | Me | Me | H | OH | H | H | H | N | S | NH | OMe | 3-N |
| 25 | Me | nPr | H | OMe | H | OMe | H | N | S | NH | OMe | 3-N |
| 26 | nPr | Me | H | OMe | H | OMe | H | N | S | NH | OMe | 3-N |
| 27 | nPr | Me | H | Me | H | Me | H | N | S | NH | OMe | 3-N |
| 28 | nPr | Me | H | OH | H | H | H | N | S | NH | OMe | 3-N |
| 29 | -(CH ₂) ₃ - | | H | OMe | H | OMe | H | N | S | NH | OMe | 3-N |
| 30 | -(CH ₂) ₃ - | | H | Me | H | Me | H | N | S | NH | OMe | 3-N |
| 31 | -(CH ₂) ₄ - | | H | OMe | H | OMe | H | N | S | NH | OMe | 3-N |
| 32 | -(CH ₂) ₄ - | | H | Me | H | Me | H | N | S | NH | OMe | 3-N |
| 33 | Me | Me | H | OMe | H | OMe | H | N | O | NH | NHMe | 3-N |
| 34 | Me | Me | H | Me | H | Me | H | N | O | NH | NHMe | 3-N |
| 35 | Me | Et | H | Me | H | Me | H | N | O | NH | NHMe | 3-N |
| 36 | -(CH ₂) ₃ - | | H | OMe | H | OMe | H | N | O | NH | NHMe | 3-N |
| 37 | -(CH ₂) ₃ - | | H | Me | H | Me | H | N | O | NH | NHMe | 3-N |
| 38 | Me | Me | H | OMe | H | OMe | H | N | O | NH |  | 3-N |
| 39 | Me | Me | H | Me | H | Me | H | N | O | NH |  | 3-N |


| Ex. No. | R ₁ | R ₂ | R ₃ | R ₄ | R ₅ | R ₆ | R ₇ | A | X | Y | Z | Y |
|---------|----------------|---|----------------|----------------|----------------|----------------|----------------|---|---|----|---|-----|
| 40 | Me | Et | H | OMe | H | OMe | H | N | O | NH |  | 3-N |
| 41 | Me | Et | H | Me | H | Me | H | N | O | NH |  | 3-N |
| 42 | Me | Me | H | OMe | H | OMe | H | N | O | NH |  | 3-N |
| 43 | Me | Me | H | Me | H | Me | H | N | O | NH |  | 3-N |
| 44 | Me | Et | H | OMe | H | OMe | H | N | O | NH |  | 3-N |
| 45 | Me | Et | H | Me | H | Me | H | N | O | NH |  | 3-N |
| 46 | Me | Ac | H | OMe | H | OMe | H | N | O | NH | OMe | 3-N |
| 47 | Me | Ac | H | Me | H | Me | H | N | O | NH | OMe | 3-N |
| 48 | Me | Ac | H | F | H | F | H | N | O | NH | OMe | 3-N |
| 49 | Me | Ac | H | Cl | H | Cl | H | N | O | NH | OMe | 3-N |
| 50 | Me | Ac | Me | Me | H | H | H | N | O | NH | OMe | 3-N |
| 51 | Me | Ac | OMe | H | H | H | H | N | O | NH | OMe | 3-N |
| 52 | Me | Ac | H | OH | H | H | H | N | O | NH | OMe | 3-N |
| 53 | Me | Ac | H | OMe | H | OMe | H | N | S | NH | OMe | 3-N |
| 54 | Me | Ac | H | Me | H | Me | H | N | S | NH | OMe | 3-N |
| 55 | Me | Ac | H | OH | H | H | H | N | S | NH | OMe | 3-N |
| 56 | Me |  | H | OMe | H | OMe | H | N | O | NH | OMe | 3-N |
| 57 | Me |  | H | Me | H | Me | H | N | O | NH | OMe | 3-N |
| 58 | Me |  | Me | Me | H | H | H | N | O | NH | OMe | 3-N |
| 59 | Me |  | H | F | H | F | H | N | O | NH | OMe | 3-N |
| 60 | Me |  | H | Cl | H | Cl | H | N | O | NH | OMe | 3-N |
| 61 | Me |  | OMe | H | H | H | H | N | O | NH | OMe | 3-N |
| 62 | Me |  | H | OH | H | H | H | N | O | NH | OMe | 3-N |
| 63 | Me |  | H | OMe | H | OMe | H | N | S | NH | OMe | 3-N |
| 64 | Me |  | H | Me | H | Me | H | N | S | NH | OMe | 3-N |

| Ex. No. | R ₁ | R ₂ | R ₃ | R ₄ | R ₅ | R ₆ | R ₇ | A | X | Y | Z | Y | |
|---------|----------------|----------------|---|----------------|----------------|----------------|----------------|---|---|---|----|-----|-----|
| 5 | 65 | Me |  | H | OMe | H | OMe | H | N | O | NH | OMe | 3-N |
| | 66 | Me |  | H | Me | H | Me | H | N | O | NH | OMe | 3-N |
| | 67 | Me |  | H | OMe | H | OMe | H | N | O | NH | OMe | 3-N |
| | 68 | Me |  | H | Me | H | Me | H | N | O | NH | OMe | 3-N |
| 10 | 69 | Me |  | H | OMe | H | OMe | H | N | O | NH | OMe | 3-N |
| | 70 | Me |  | H | Me | H | Me | H | N | O | NH | OMe | 3-N |
| | 71 | Me |  | H | OMe | H | OMe | H | N | O | NH | OMe | 3-N |
| 15 | 72 | Me |  | H | Me | H | Me | H | N | O | NH | OMe | 3-N |
| | 73 | Me | Vinyl | H | OMe | H | OMe | H | N | O | NH | OMe | 3-N |
| | 74 | Me | Vinyl | H | Me | H | Me | H | N | O | NH | OMe | 3-N |
| 20 | 75 | Me | Vinyl | H | F | H | F | H | N | O | NH | OMe | 3-N |
| | 76 | Me |  | H | OMe | H | OMe | H | N | O | NH | OMe | 3-N |
| | 77 | Me |  | H | Me | H | Me | H | N | O | NH | OMe | 3-N |
| 25 | 78 | Me |  | H | OMe | H | OMe | H | N | O | NH | OMe | 3-N |
| | 79 | Me |  | H | OMe | H | OMe | H | N | O | NH | OMe | 3-N |
| 30 | 80 | Me |  | H | Me | H | Me | H | N | O | NH | OMe | 3-N |

| Ex. No. | R ₁ and R ₂ | R ₃ | R ₄ | R ₅ | R ₆ | R ₇ | R ₈ | A | X | Z | Y | |
|---------|-----------------------------------|----------------|----------------|---|----------------|----------------|----------------|---|---|---|-----|-----|
| 5 | 81 | -CH=CH-CH=CH- | H | OMe | H | OMe | H | H | N | O | OMe | 3-N |
| | 82 | -CH=CH-CH=CH- | H | Me | H | Me | H | H | N | O | OMe | 3-N |
| | 83 | -CH=CH-CH=CH- | Me | Me | H | H | H | H | N | O | OMe | 3-N |
| | 84 | -CH=CH-CH=CH- | H | F | H | F | H | H | N | O | OMe | 3-N |
| | 85 | -CH=CH-CH=CH- | H | Cl | H | Cl | H | H | N | O | OMe | 3-N |
| 10 | 86 | -CH=CH-CH=CH- | F | H | H | H | H | H | N | O | OMe | 3-N |
| | 87 | -CH=CH-CH=CH- | Cl | H | H | H | H | H | N | O | OMe | 3-N |
| | 88 | -CH=CH-CH=CH- | H | Cl | H | H | H | H | N | O | OMe | 3-N |
| | 89 | -CH=CH-CH=CH- | H | OH | H | H | H | H | N | O | OMe | 3-N |
| 15 | 90 | -CH=CH-CH=CH- | OMe | H | H | H | H | H | N | O | OMe | 3-N |
| | 91 | -CH=CH-CH=CH- | SMe | H | H | H | H | H | N | O | OMe | 3-N |
| | 92 | -CH=CH-CH=CH- | H |  | H | H | H | H | N | O | OMe | 3-N |
| 20 | 93 | -CH=CH-CH=CH- | H |  | H | H | H | H | N | O | OMe | 3-N |
| | 94 | -CH=CH-CH=CH- | OMe | H | H | Me | H | H | N | O | OMe | 3-N |
| | 95 | -CH=CH-CH=CH- | OMe | H | H | Ph | H | H | N | O | OMe | 3-N |
| | 96 | -CH=CH-CH=CH- | Me | H | H | OMe | H | H | N | O | OMe | 3-N |
| 25 | 97 | -CH=CH-CH=CH- | -Benzo- | | H | H | H | H | N | O | OMe | 3-N |
| | 98 | -CH=CH-CH=CH- | H | OMe | H | OMe | H | Me | N | O | OMe | 3-N |
| | 99 | -CH=CH-CH=CH- | H | OMe | H | OMe | H | Et | N | O | OMe | 3-N |
| | 100 | -CH=CH-CH=CH- | H | OMe | H | OMe | H | iPr | N | O | OMe | 3-N |
| 30 | 101 | -CH=CH-CH=CH- | H | OMe | H | OMe | H |  | N | O | OMe | 3-N |
| | 102 | -CH=CH-CH=CH- | H | OMe | H | OMe | H | Benzyl | N | O | OMe | 3-N |
| | 103 | -CH=CH-CH=CH- | H | Me | H | Me | H | Me | N | O | OMe | 3-N |
| 35 | 104 | -CH=CH-CH=CH- | H | Me | H | Me | H | Et | N | O | OMe | 3-N |
| | 105 | -CH=CH-CH=CH- | H | Me | H | Me | H | iPr | N | O | OMe | 3-N |

| | Ex. No | R ₁ and R ₂ | R ₃ | R ₄ | R ₅ | R ₆ | R ₇ | R ₈ | A | X | Z | Y |
|----|-----------|-----------------------------------|----------------|---|----------------|----------------|----------------|----------------|---|---|-----------|-----|
| 5 | 106 | -CH=CH-CH=CH- | H | Me | H | Me | H | Ben zyl | N | O | OMe | 3-N |
| | 107 | -CH=CH-CH=CH- | H |  | H | H | H | Me | N | O | OMe | 3-N |
| | 108 | -CH=CH-CH=CH- | H |  | H | H | H | Et | N | O | OMe | 3-N |
| | 109 | -CH=CH-CH=CH- | H | OMe | H | OMe | H | H | N | S | OMe | 3-N |
| 10 | 110 | -CH=CH-CH=CH- | H | Me | H | Me | H | H | N | S | OMe | 3-N |
| | 111 | -CH=CH-CH=CH- | H | F | H | F | H | H | N | S | OMe | 3-N |
| | 112 | -CH=CH-CH=CH- | H | Cl | H | Cl | H | H | N | S | OMe | 3-N |
| | 113 | -CH=CH-CH=CH- | H | OMe | H | H | H | H | N | S | OMe | 3-N |
| 15 | 114 | -CH=CH-CH=CH- | H | OMe | H | OMe | H | H | N | O | Me | 3-N |
| | 115 | -CH=CH-CH=CH- | H | Me | H | Me | H | H | N | O | Me | 3-N |
| | 116 | -CH=CH-CH=CH- | Me | Me | H | H | H | H | N | O | Me | 3-N |
| | 117 | -CH=CH-CH=CH- | H | F | H | F | H | H | N | O | Me | 3-N |
| 20 | 118 | -CH=CH-CH=CH- | H | Cl | H | Cl | H | H | N | O | Me | 3-N |
| | 119 | -CH=CH-CH=CH- | OMe | H | H | H | H | H | N | O | Me | 3-N |
| | 120 | -CH=CH-CH=CH- | F | H | H | H | H | H | N | O | Me | 3-N |
| | 121 | -CH=CH-CH=CH- | Cl | H | H | H | H | H | N | O | Me | 3-N |
| 25 | 122 | -CH=CH-CH=CH- | SMe | H | H | H | H | H | N | O | Me | 3-N |
| | 123 | -CH=CH-CH=CH- | OMe | H | H | Me | H | H | N | O | Me | 3-N |
| | 124 | -CH=CH-CH=CH- | -Benzo- | | H | H | H | H | N | O | Me | 3-N |
| | 125 | -CH=CH-CH=CH- | H | OMe | H | OMe | H | H | N | S | Me | 3-N |
| 30 | 126 | -CH=CH-CH=CH- | H | Me | H | Me | H | H | N | S | Me | 3-N |
| | 127 | -CH=CH-CH=CH- | H | F | H | F | H | H | N | S | Me | 3-N |
| | 128 | -CH=CH-CH=CH- | H | OMe | H | OMe | H | H | N | O | 2-Py | 4-N |
| | 129 | -CH=CH-CH=CH- | H | OMe | H | OMe | H | H | N | O | 3-Py | 4-N |
| 35 | 130 | -CH=CH-CH=CH- | H | OMe | H | OMe | H | H | N | O | 2-Thienyl | 4-N |
| | 131 | -CH=CH-CH=CH- | H | Me | H | Me | H | H | N | O | 3-Py | 4-N |




















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| Ex. No. | R ₁ | R ₂ | R ₃ | R ₄ | R ₅ | R ₆ | R ₇ | R ₈ | A | X | Z | Y | |
|---------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|---|------|---|-----|-----|-----|
| 5 | 132 | Me | Me | H | OMe | H | OMe | H | Me | N | O | OMe | 3-N |
| | 133 | Me | Me | H | OMe | H | OMe | H | Et | N | O | OMe | 3-N |
| | 134 | Me | Me | H | OMe | H | OMe | H | i-Pr | N | O | OMe | 3-N |
| | 135 | Me | Me | H | Me | H | Me | H | Me | N | O | OMe | 3-N |
| | 136 | Me | Me | OMe | H | H | H | H | Me | N | O | OMe | 3-N |
| 10 | 137 | Me | Me | OMe | H | H | H | H | Et | N | O | OMe | 3-N |
| | 138 | Me | Me | OMe | H | H | H | H | Bn | N | O | OMe | 3-N |
| | 139 | Me | Me | OMe | H | H | H |  | N | O | OMe | 3-N | |
| | 140 | Me | Me | Me | H | H | OMe | H | Me | N | O | OMe | 3-N |
| 15 | 141 | Me | Me | Me | H | H | OMe | H | Et | N | O | OMe | 3-N |
| | 142 | Me | Me | Me | H | H | OMe | H | Bn | N | O | OMe | 3-N |
| | 143 | Me | Et | H | OMe | H | OMe | H | Me | N | O | OMe | 3-N |
| 20 | 144 | Me | Et | H | Me | H | Me | H | Me | N | O | OMe | 3-N |
| | 145 | Me | Et | H | Me | H | Me | H | Et | N | O | OMe | 3-N |


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



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





35

| Ex. No. | R ₁ | R ₂ | R ₃ | R ₄ | R ₅ | R ₆ | R ₇ | R ₈ | A | X | Z | Y | |
|---------|----------------|----------------|---|----------------|----------------|----------------|----------------|----------------|--|---|---|-----|-----|
| 5 | 146 | Me | nPr | H | OMe | H | OMe | H | Me | N | O | OMe | 3-N |
| | 147 | Et | Me | H | OMe | H | OMe | H | Me | N | O | OMe | 3-N |
| | 148 | nPr | Me | H | OMe | H | OMe | H | Me | N | O | OMe | 3-N |
| | 149 | Me | Ac | H | OMe | H | OMe | H | Me | N | O | OMe | 3-N |
| | 150 | Me | Ac | H | OMe | H | OMe | H | Et | N | O | OMe | 3-N |
| 10 | 151 | Me | Ac | H | Me | H | Me | H | Me | N | O | OMe | 3-N |
| | 152 | Me |  | H | OMe | H | OMe | H | Me | N | O | OMe | 3-N |
| | 153 | Me |  | H | OMe | H | OMe | H | Et | N | O | OMe | 3-N |
| | 154 | Me |  | H | Me | H | Me | H | Me | N | O | OMe | 3-N |
| 15 | 155 | Me |  | H | OMe | H | OMe | H | Me | N | O | OMe | 3-N |
| | 156 | Me |  | H | Me | H | Me | H | Me | N | O | OMe | 3-N |
| | 157 | Me |  | H | OMe | H | OMe | H | Me | N | O | OMe | 3-N |
| | 158 | Me | Vinyl | H | OMe | H | OMe | H | Me | N | O | OMe | 3-N |
| 20 | 159 | Me | Vinyl | H | Me | H | Me | H | Me | N | O | OMe | 3-N |
| | 160 | Me | Vinyl | H | OMe | H | OMe | H | Et | N | O | OMe | 3-N |
| | 161 | Me |  | H | OMe | H | OMe | H | Me | N | O | OMe | 3-N |
| | 162 | Me |  | H | Me | H | Me | H | Me | N | O | OMe | 3-N |
| 25 | 163 | Me | Ac | H | OMe | H | OMe | H |  | N | O | OMe | 3-N |
| | 164 | Me | Ac | H | Me | H | Me | H |  | N | O | OMe | 3-N |
| | 165 | Me | Ac | H | OMe | H | OMe | H |  | N | O | OMe | 3-N |
| | 166 | Me |  | H | OMe | H | OMe | H |  | N | O | OMe | 3-N |
| 30 | 167 | Me |  | H | OMe | H | OMe | H |  | N | O | OMe | 3-N |
| | 168 | Me |  | H | Me | H | Me | H |  | N | O | OMe | 3-N |
| | 169 | Me |  | H | Me | H | Me | H |  | N | O | OMe | 3-N |
| | | | | | | | | | | | | | |

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| | Ex. No. | R ₁ | R ₂ | R ₃ | R ₄ | R ₅ | R ₆ | R ₇ | R ₈ | A | X | Z | Y |
|----|------------|----------------|----------------|---|----------------|----------------|----------------|----------------|----------------|----|---|-----|-----|
| 5 | 170 | Me | Me | H | H | H | H | H | H | CH | O | OMe | 3-N |
| | 171 | Me | Me | H | OMe | H | OMe | H | H | CH | O | OMe | 3-N |
| | 172 | Me | Me | H | Me | H | Me | H | H | CH | O | OMe | 3-N |
| | 173 | Me | Me | Me | Me | H | H | H | H | CH | O | OMe | 3-N |
| | 174 | Me | Me | Me | Me | H | Me | Me | H | CH | O | OMe | 3-N |
| 10 | 175 | Me | Me | H | F | H | F | H | H | CH | O | OMe | 3-N |
| | 176 | Me | Me | Cl | H | H | H | H | H | CH | O | OMe | 3-N |
| | 177 | Me | Me | H | Cl | H | H | H | H | CH | O | OMe | 3-N |
| | 178 | Me | Me | OH | H | H | H | H | H | CH | O | OMe | 3-N |
| | 179 | Me | Me | H | OH | H | H | H | H | CH | O | OMe | 3-N |
| 15 | 180 | Me | Me | H | SH | H | H | H | H | CH | O | OMe | 3-N |
| | 181 | Me | Me | OAc | H | H | H | H | H | CH | O | OMe | 3-N |
| | 182 | Me | Me | H | OAc | H | H | H | H | CH | O | OMe | 3-N |
| | 183 | Me | Me | OMe | H | H | H | H | H | CH | O | OMe | 3-N |
| | 184 | Me | Me | H | Me | H | H | OMe | H | CH | O | OMe | 3-N |
| 20 | 185 | Me | Me | H | OMe | H | H | Me | H | CH | O | OMe | 3-N |
| | 186 | Me | Me | H | OMe | H | H | Ph | H | CH | O | OMe | 3-N |
| | 187 | Me | Me |  | H | H | H | H | H | CH | O | OMe | 3-N |
| | 188 | Me | Me | Benzo | | H | H | H | H | CH | O | OMe | 3-N |
| | 189 | Me | Me | Naphto | | H | H | H | H | CH | O | OMe | 3-N |
| 25 | 190 | Me | Me | H | OMe | H | OMe | H | Me | CH | O | OMe | 3-N |
| | 191 | Me | Me | H | Me | H | Me | H | Me | CH | O | OMe | 3-N |
| | 192 | Me | Me | H | F | H | F | H | Me | CH | O | OMe | 3-N |
| | 193 | Me | Me | H | OMe | H | OMe | H | Et | CH | O | OMe | 3-N |
| | 194 | Me | Me | H | Me | H | Me | H | Et | CH | O | OMe | 3-N |
| 30 | | | | | | | | | | | | | |
| 35 | | | | | | | | | | | | | |

| Ex. No. | R ₁ | R ₂ | R ₃ | R ₄ | R ₅ | R ₆ | R ₇ | R ₈ | A | X | Z | Y |
|---------|----------------|---|--|----------------|----------------|----------------|----------------|----------------|----|---|-----|-----|
| 195 | Me | Me | H | F | H | F | H | Et | CH | O | OMe | 3-N |
| 196 | Me | Me | H | F | H | F | H | iPr | CH | O | OMe | 3-N |
| 197 | Me | Me | H | OMe | H | OMe | H | H | CH | S | OMe | 3-N |
| 198 | Me | Me | H | Me | H | Me | H | H | CH | S | OMe | 3-N |
| 199 | Me | Me | Me | Me | H | H | H | H | CH | S | OMe | 3-N |
| 200 | Me | Me | H | F | H | F | H | H | CH | S | OMe | 3-N |
| 201 | Me | Me | H | Cl | H | Cl | H | H | CH | S | OMe | 3-N |
| 202 | Me | Me | F | H | H | H | H | H | CH | S | OMe | 3-N |
| 203 | Me | Me | Cl | H | H | H | H | H | CH | S | OMe | 3-N |
| 204 | Me | Me | OMe | H | H | H | H | H | CH | S | OMe | 3-N |
| 205 | Me | Me | SMe | H | H | H | H | H | CH | S | OMe | 3-N |
| 206 | Me | Me | H | OH | H | H | H | H | CH | S | OMe | 3-N |
| 207 | Me | Me | OPh | H | H | H | H | H | CH | S | OMe | 3-N |
| 208 | Me | Me |  | H | H | H | H | H | CH | S | OMe | 3-N |
| 209 | Me | Me | H | OMe | H | H | Me | H | CH | S | OMe | 3-N |
| 210 | Me | Me | Benzo | | H | H | H | H | CH | S | OMe | 3-N |
| 211 | Me | Acetyl | H | OMe | H | OMe | H | H | CH | O | OMe | 3-N |
| 212 | Me | Acetyl | H | Me | H | Me | H | H | CH | O | OMe | 3-N |
| 213 | Me | Acetyl | H | Cl | H | Cl | H | H | CH | O | OMe | 3-N |
| 214 | Me |  | H | OMe | H | OMe | H | H | CH | O | OMe | 3-N |
| 215 | Me |  | H | Me | H | Me | H | H | CH | O | OMe | 3-N |
| 216 | Me | Vinyl | H | OMe | H | OMe | H | H | CH | O | OMe | 3-N |
| 217 | Me | Vinyl | H | Me | H | Me | H | H | CH | O | OMe | 3-N |
| 218 | Me | Acetyl | H | OMe | H | OMe | H | H | CH | S | OMe | 3-N |
| 219 | Me | Acetyl | H | Me | H | Me | H | H | CH | S | OMe | 3-N |
| 220 | Me | Acetyl | H | Cl | H | Cl | H | H | CH | S | OMe | 3-N |
| 221 | Me |  | H | OMe | H | OMe | H | H | CH | S | OMe | 3-N |

| Ex. No. | R ₁ | R ₂ | R ₃ | R ₄ | R ₅ | R ₆ | R ₇ | R ₈ | A | X | Z | Y |
|------------|----------------|---|----------------|----------------|----------------|----------------|----------------|---|----|---|-----|-----|
| 222 | Me |  | H | Me | H | Me | H | H | CH | S | OMe | 3-N |
| 223 | Me |  | H | Cl | H | Cl | H | H | CH | S | OMe | 3-N |
| 224 | Me | Me | H | OMe | H | OMe | H |  | CH | O | OMe | 3-N |
| 225 | Me | Me | H | Me | H | Me | H |  | CH | O | OMe | 3-N |
| 226 | Me | Me | H | OMe | H | OMe | H |  | CH | O | OMe | 3-N |
| 227 | Me | Me | H | Me | H | Me | H |  | CH | O | OMe | 3-N |
| 228 | Me | Me | H | OMe | H | OMe | H | H | CH | O | OH | 3-N |
| 229 | Me | Me | H | Me | H | Me | H | H | CH | O | OH | 3-N |
| 230 | Me | Me | H | F | H | F | H | H | CH | O | OH | 3-N |
| 231 | Me | Me | H | Cl | H | Cl | H | H | CH | O | OH | 3-N |

Example 1

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methylthio phenyl)piperazine:

- 5 a) Phenyl N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate:
3-Amino-5,6-dimethyl-2-methoxypyridine(1.52g, 0.01mol) and
phenylchloroformate(1.56g, 0.01mol) were dissolved in dichloromethane
and was stirred at room temperature for 2 hours. The mixture was
concentrated under the reduced pressure to remove the solvent. The
10 concentrate was purified by column chromatography(ethylacetate :
hexane = 1:6) to obtain the titled compound.
yield: 92 %
¹H-NMR(CDCl₃) δ : 2.18(3H,s), 2.36(3H,s), 4.00(3H,s), 7.31(5H,m),
8.07(1H,s)

- 15 b) 1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methyl
thiophenyl)piperazine:
Phenyl N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate(136mg,
0.5mmol) and 1-(2-methylthiophenyl)piperazine(104mg, 0.5mmol) were
20 dissolved in anhydrous tetrahydrofuran and DBU(76mg, 0.5mmol) was
added. The mixture was stirred at room temperature for 2 hours and
concentrated under the reduced pressure to remove tetrahydrofuran. The
concentrate was purified by column chromatography(ethylacetate :
hexane = 1 : 2) to obtain the titled compound.
25 yield : 59%
m.p. : 167-169°C
¹H NMR(CDCl₃) δ : 2.21(3H,s), 2.43(6H,s), 3.06(4H,t), 3.68(4H,t),
4.09(3H,s), 6.89(1H,s), 7.06(1H,m), 7.14(3H,s), 8.26(1H,s)

30 Example 2

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-isopropenyl
phenyl)piperazine :

- Phenyl N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate and
1-(2-isopropenylphenyl)piperazine were reacted by the same way with
35 the example 1 to obtain the titled compound.
yield: 62 %

- 21 -

m.p. : 139-140°C

¹H NMR(CDCl₃) δ : 2.20(3H,s), 2.21(6H,s), 3.10(4H,t), 3.64(4H,t),
3.84(3H,s), 5.07(1H,s), 5.13(1H,s), 6.64(1H,s), 6.98(1H,s), 7.04(3H,dd),
7.18(1H,d), 7.91(1H,s)

5

Example 3

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2,3,5,6-tetramethylphenyl)piperazine:

Phenyl N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate and

10 1-(2,3,5,6-tetramethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 71%

m.p. : 190-192°C

¹H NMR(CDCl₃) δ : 2.21(15H,s), 2.42(3H,s), 3.17(4H,t), 3.61(4H,t),
15 4.08(3H,s), 6.84(1H,s), 6.89(1H,s), 8.26(1H,s)

Example 4

1-[(5-Ethyl-6-methyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methylthiophenyl)piperazine:

20 Phenyl N-(5-ethyl-6-methyl-2-methoxypyridin-3-yl)carbamate and 1-(2-methylthiophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 56%

m.p. : 160-161°C

¹H NMR(CDCl₃) δ : 1.19(3H,t), 2.43(3H,s), 2.50(3H,s), 2.58(2H,q),
25 3.07(4H,t), 3.69(4H,t), 4.15(3H,s), 6.93(1H,s), 7.06(1H,m), 7.14(3H,m),
8.35(1H,s)

Mass(EI) m/z : Calcd for C₂₁H₂₈N₄O₂ 400.1932, found 400.1925

30 Example 5

1-[(5-Ethyl-6-methyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-isopropenylphenyl)piperazine:

Phenyl N-(5-ethyl-6-methyl-2-methoxypyridin-3-yl)carbamate and

1-(2-isopropenylphenyl)piperazine were reacted by the same way with
35 the example 1 to obtain the titled compound.

yield : 51%

- 22 -

m.p. : 185-187°C

¹H NMR(CDCl₃) δ : 1.18(3H,t), 2.21(3H,s), 2.42(3H,s), 2.56(2H,q),
3.08(4H,t), 3.62(4H,t), 4.03(3H,s), 5.08(1H,s), 5.13(1H,s), 6.90(1H,s),
7.02(3H,m), 7.18(1H,d), 8.25(1H,s)

5

Example 6

1-[(5-Ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2,3,5,6-tetramethylphenyl)piperazine:

Phenyl N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and
10 1-(2,3,5,6-tetramethylphenyl)piperazine were reacted by the same way
with the example 1 to obtain the titled compound.

yield : 69%

m.p. : 176-177°C

¹H NMR(CDCl₃) δ : 1.19(3H,t), 2.21(12H,s), 2.44(3H,s), 2.57(2H,q),
15 3.17(4H,t), 3.62(4H,t), 4.06(3H,s), 6.84(1H,s), 6.92(1H,s), 8.30(1H,s)

Example 7

1-[(5-Ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3-thiophenyl)piperazine:

20 Phenyl N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and
1-(3-thiophenyl)piperazine were reacted by the same way with the
example 1 to obtain the titled compound.

yield : 63%

m.p. : 108-110°C

¹H NMR(CDCl₃) δ : 1.17(3H,t), 2.37(3H,s), 2.49(2H,q), 3.28(4H,t),
25 3.60(4H,t), 3.98(3H,s), 6.87(4H,m), 6.98(1H,s), 8.18(1H,s)

Example 8

1-[(2-Methoxy-6-methyl-5-propylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(2-methoxy-6-methyl-5-propylpyridin-3-yl)carbamate and
1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with
the example 1 to obtain the titled compound.

yield : 67%

35 m.p. : 82-84°C

¹H NMR(CDCl₃) δ : 0.94(3H,t), 1.58(2H,m), 2.37(3H,s), 2.49(2H,q),

- 23 -

3.25(4H,t), 3.66(4H,t), 3.78(6H,s), 3.99(3H,s), 6.07(3H,m), 6.88(1H,s),
8.16(1H,s)

Mass(EI) m/z : Calcd for $C_{23}H_{32}N_4O_1$ 428.2423, found 428.2447

5 Example 9

1-[(2-Methoxy-6-methyl-5-propylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine

Phenyl N-(2-methoxy-6-methyl-5-propylpyridin-3-yl)carbamate and
1-(3,5-dimethylphenyl)piperazine were reacted by the same way with
10 the example 1 to obtain the titled compound.

yield : 64%

m.p. : 145-146°C

^1H NMR(CDCl_3) δ : 0.95(3H,t), 1.59(2H,m), 2.29(6H,s), 2.41(3H,s),
2.49(2H,q), 3.24(4H,t), 3.67(4H,t), 3.98(3H,s), 6.59(3H,m), 6.89(1H,s),
15 8.17(1H,s)

Mass(EI) m/z : Calcd for $C_{23}H_{32}N_4O_4$ 428.2423, found 428.2385

Example 10

1-[(2-Methoxy-6-methyl-5-propylpyridin-3-yl)aminocarbonyl]-4-(3,5-difluorophenyl)piperazine:

Phenyl N-(2-methoxy-6-methyl-5-propylpyridin-3-yl)carbamate and
1-(3,5-difluorophenyl)piperazine were reacted by the same way with the
example 1 to obtain the titled compound.

yield : 57%

25 m.p. : 121-123°C

^1H NMR(CDCl_3) δ : 0.95(3H,t), 1.59(2H,m), 2.38(3H,s), 2.50(2H,q),
3.29(3H,t), 3.66(3H,t), 4.00(3H,s), 6.28(1H,m), 6.36(2H,d), 6.87(1H,s),
8.17(1H,s)

30 Example 11

1-[(2-Methoxy-6-methyl-5-propylpyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine:

Phenyl N-(2-methoxy-6-methyl-5-propylpyridin-3-yl)carbamate and
1-(2-methoxyphenyl)piperazine were reacted by the same way with the
35 example 1 to obtain the titled compound.

yield : 71%

- 24 -

m.p. : 109-110°C

¹H NMR(CDCl₃) δ : 0.95(3H,t), 1.59(2H,m), 2.37(3H,s), 2.49(2H,q),
3.12(4H,t), 3.70(4H,t), 3.89(3H,s), 3.97(3H,s), 6.91(4H,m), 6.95(1H,s),
5 8.19(1H,s)

Example 12

1-[(6-Ethyl-2-methoxy-5-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

10 Phenyl N-(6-ethyl-2-methoxy-5-methylpyridin-3-yl)carbamate and
1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with
the example 1 to obtain the titled compound.

yield : 65%

m.p. : 115-116°C

15 ¹H NMR(CDCl₃) δ : 1.21(3H,t), 2.21(3H,s), 2.65(2H,q), 3.27(4H,t),
3.64(4H,t), 3.79(6H,s), 3.98(3H,s), 6.09(3H,m), 6.86(1H,s), 8.12(1H,s)

Mass(EI) m/z : Calcd for C₂₂H₃₀N₄O₄ 414.2267, found 414.2240

Example 13

20 1-[(6-Ethyl-2-methoxy-5-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-(6-ethyl-2-methoxy-5-methylpyridin-3-yl)carbamate and
1-(3,5-dimethylphenyl)piperazine were reacted by the same way with
the example 1 to obtain the titled compound.

25 yield : 61%

m.p. : 135-136°C

¹H NMR(CDCl₃) δ : 1.22(3H,t), 2.21(3H,s), 2.29(6H,s), 2.65(2H,q),
3.24(4H,t), 3.66(4H,t), 3.98(3H,s), 6.59(3H,m), 6.87(1H,s), 8.12(1H,s)

Mass(EI) m/z : Calcd for C₂₂H₃₀N₄O₂ 382.2368, found 382.2376

30

Example 14

1-[(6-Ethyl-2-methoxy-5-methylpyridin-3-yl)aminocarbonyl]-4-(3-hydroxyphenyl)piperazine:

Phenyl N-(6-ethyl-2-methoxy-5-methylpyridin-3-yl)carbamate and
35 1-(3-hydroxyphenyl)piperazine were reacted by the same way with the
example 1 to obtain the titled compound.

- 25 -

yield : 56%

m.p. : 168-170°C

¹H NMR(CDCl₃) δ : 1.21(3H,t), 2.20(2H,s), 2.63(2H,t), 3.28(4H,t), 3.68(4H,t),
3.98(3H,s), 6.41(1H,d), 6.55(1H,d), 6.84(1H,m), 6.87(1H,s), 7.13(1H,t),
8.10(1H,s)

Mass(EI) m/z : Calcd for C₂₀H₂₆N₄O₃ 370.2004, found 370.1992

Example 15

1-[(2-Methoxy-5-methyl-6-propylpyridin-3-yl)aminocarbonyl]-4-(3,5-
dimethoxyphenyl)piperazine:

Phenyl N-(2-methoxy-5-methyl-6-propylpyridin-3-yl)carbamate and
1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with
the example 1 to obtain the titled compound.

yield : 57%

m.p : 121-122°C

¹H NMR(CDCl₃) δ : 0.96(3H,t), 1.67(2H,m), 2.21(3H,s), 2.58(2H,t),
3.26(4H,t), 3.68(4H,t), 3.79(6H,s), 3.97(3H,s), 6.14(3H,m), 6.89(1H,s),
8.11(1H,s)

Mass(EI) m/z : Calcd for C₂₃H₃₂N₄O₄ 428.2423, found 428.2423

Example 16

1-[(2-Methoxy-5-methyl-6-propylpyridin-3-yl)aminocarbonyl]-4-(3,5-di-
methylphenyl)piperazine:

Phenyl N-(2-methoxy-5-methyl-6-propylpyridin-3-yl)carbamate and
1-(3,5-dimethylphenyl)piperazine were reacted by the same way with
the example 1 to obtain the titled compound.

yield : 54%

m.p. : 138-139°C

¹H NMR(CDCl₃) δ : 0.96(3H,t), 1.72(2H,m), 2.21(6H,s), 2.30(3H,s),
2.59(2H,t), 3.28(4H,t), 3.76(4H,t), 3.97(3H,s), 6.70(3H,m), 6.87(1H,s),
8.11(1H,s)

Mass(EI) m/z : Calcd for C₂₃H₃₂N₄O₂ 396.2525, found 396.2432

Example 17

1-[(2-Methoxy-5-methyl-6-propylpyridin-3-yl)aminocarbonyl]-4-(3-
hydroxyphenyl)piperazine:

Phenyl N-(2-methoxy-5-methyl-6-propylpyridin-3-yl)carbamate and 1-(3-hydroxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 52%

5 m.p. : 153-155°C

¹H NMR(CDCl₃) δ : 0.95(3H,t), 1.69(2H,m), 2.19(3H,s), 2.59(2H,t), 3.22(4H,t), 3.68(4H,t), 3.97(3H,s), 6.42(1H,d), 6.52(1H,d), 6.87(1H,s), 7.12(1H,t), 8.09(1H,s)

Mass(EI) m/z : Calcd for C₂₁H₂₈N₄O₃ 384.2161, found 384.2153

10

Example 18

1-[N-(2-Methoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(2-methoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)

15 carbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 59%

m.p. : 143-144°C

¹H NMR(CDCl₃) δ : 2.10(2H,m), 2.87(4H,m), 3.12(4H,t), 3.70(4H,t),
20 3.78(6H,s), 4.00(3H,s), 6.08(3H,m), 6.90(1H,s), 8.24(1H,s)

Example 19

1-[N-(2-Methoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

25 Phenyl N-(2-methoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 55%

m.p. : 183-185°C

30 ¹H NMR(CDCl₃) δ : 2.08(2H,m), 2.28(6H,s), 2.87(4H,m), 3.22(4H,t), 3.67(4H,t), 4.00(3H,s), 6.57(3H,m), 6.89(1H,s), 8.24(1H,s)

Example 20

1-[(2-Methoxy-5,6,7,8-tetrahydroquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

35 Phenyl N-(2-methoxy-5,6,7,8-tetrahydroquinoline-3-yl)carbamate and

- 27 -

1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 54%

m.p. : 161-163°C

- 5 ^1H NMR(CDCl_3) δ : 1.75(2H,m), 1.84(2H,m), 2.67(2H,t), 2.73(2H,t), 3.27(4H,t), 3.71(4H,t), 3.79(6H,s), 3.97(3H,s), 6.10(3H,m), 6.90(1H,s), 8.07(1H,s)

Example 21

- 10 1-[(2-Methoxy-5,6,7,8-tetrahydroquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-(2-methoxy-5,6,7,8-tetrahydroquinolin-3-yl)carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

- 15 yield : 51%

m.p. : 143-144°C

^1H NMR(CDCl_3) δ : 1.75(2H,m), 1.84(2H,m), 2.30(6H,s), 2.68(2H,t), 2.72(2H,t), 3.26(4H,t), 3.67(4H,t), 3.97(3H,s), 6.61(3H,m), 6.91(1H,s), 8.07(1H,s)

20

Example 22

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminothiocabonyl]-4-(3,5-dimethylphenyl)piperazine:

- Phenyl N-(5,6-dimethyl-2-methoxypyridin-3-yl)thiocarbamate(200mg, 0.7mmol) and 1-(3,5-dimethylphenyl)piperazine(154mg, 0.7mmol) were dissolved in anhydrous tetrahydrofuran and DBU(106mg) was added thereto. The mixture was stirred at room temperature for 2 hours and concentrated under the reduced pressure to remove the solvent. The concentrate was purified by column chromatography(ethylacetate :
25 hexane = 1 : 2) to obtain the titled compound.

30 yield : 50%

m.p. : 192-193°C

^1H NMR(CDCl_3) δ : 2.21(3H,s), 2.29(6H,s), 2.36(3H,s), 3.33(4H,t), 3.96(3H,s), 4.09(4H,t), 6.57(3H,m), 7.33(1H,s), 8.11(1H,s)

- 35 Mass(EI) m/z : Calcd for $\text{C}_{21}\text{H}_{28}\text{N}_4\text{O}_1\text{S}_1$ 384.1983, found 384.1992

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Example 23

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminothiocarbonyl]-4-(3,5-difluorophenyl)piperazine:

- 5 Phenyl N-(5,6-dimethyl-2-methoxypyridin-3-yl)thiocarbamate and 1-(3,5-difluorophenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.

yield : 47%

m.p. : 60-62°C

- 10 ^1H NMR(CDCl_3) δ : 2.21(3H,s), 2.36(3H,s), 3.39(4H,t), 3.96(3H,s), 4.10(3H,t), 6.29(3H,m), 7.33(1H,s), 8.14(1H,s)

Example 24

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminothiocarbonyl]-4-(3-hydroxyphenyl)piperazine:

- 15 Phenyl N-(5,6-dimethyl-2-methoxypyridin-3-yl)thiocarbamate and 1-(3-hydroxyphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.

yield : 43%

m.p. : 185-186°C

- 20 ^1H NMR(CDCl_3) δ : 2.14(3H,s), 2.36(3H,s), 3.25(4H,t), 3.89(3H,s), 4.09(4H,t), 6.30(1H,d), 6.36(2H,m), 7.03(1H,t), 7.48(1H,s), 8.56(1H,s)

Example 25

- 25 1-[(2-Methoxy-6-methyl-5-propylpyridin-3-yl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(2-methoxy-6-methyl-5-propylpyridin-3-yl)thiocarbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.

yield : 55%

- 30 m.p. : 143-144°C

^1H NMR(CDCl_3) δ : 0.93(3H,t), 1.66(2H,m), 2.17(3H,s), 2.65(2H,t), 3.38(4H,t), 3.79(6H,s), 3.98(3H,s), 4.15(4H,t), 6.11(3H,m), 7.43(1H,s), 8.25(1H,s)

35 Example 26

1-[(2-Methoxy-5-methyl-6-propylpyridin-3-yl)aminothiocarbonyl]-4-(3,5

- 29 -

-dimethoxyphenyl)piperazine:

Phenyl N-(2-methoxy-5-methyl-6-propylpyridin-3-yl)thiocarbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.

5 yield : 52%

m.p. : 183-184°C

¹H NMR(CDCl₃) δ : 0.98(3H,t), 1.72(2H,m), 2.17(3H,s), 2.62(2H,t), 3.39(4H,t), 3.79(6H,s), 3.96(3H,s), 4.19(4H,t), 6.15(3H,m), 7.42(1H,s), 8.08(1H,s)

10 Mass(EI) m/z : Calcd for C₂₃H₃₂N₄O₃S₁ 444.2195, found 444.2171

Example 27

1-[(2-Methoxy-5-methyl-6-propylpyridin-3-yl)aminothi carbonyl]-4-(3,5-dimethylphenyl)piperazine:

15 Phenyl N-(2-methoxy-5-methyl-6-propylpyridin-3-yl)thiocarbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.

yield : 49%

m.p. : 195-197°C

20 ¹H NMR(CDCl₃) δ : 0.98(3H,t), 1.73(2H,m), 2.18(6H,s), 2.34(3H,s), 2.62(2H,t), 3.47(4H,t), 3.96(3H,s), 4.01(4H,t), 6.59(3H,m), 7.02(1H,s), 7.99(1H,s)

Mass(EI) m/z : Calcd for C₂₃H₃₂N₄O₁S₁ 412.2296, found 412.2266

25 Example 28

1-[(2-Methoxy-5-methyl-6-propylpyridin-3-yl)aminothi carbonyl]-4-(3-hydroxyphenyl)piperazine:

30 Phenyl N-(2-methoxy-5-methyl-6-propylpyridin-3-yl)thiocarbamate and 1-(3-hydroxyphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.

yield : 48%

m.p. : 160-162°C

35 ¹H NMR(CDCl₃) δ : 0.98(3H,t), 1.72(2H,m), 2.22(3H,s), 2.61(3H,t), 3.31(4H,t), 3.95(3H,s), 4.10(4H,t), 6.45(3H,m), 7.12(1H,t), 7.41(1H,s), 8.08(1H,s)

Mass(EI) m/z : Calcd for C₂₁H₂₈N₄O₂S₁ 400.1932, found 400.1969

Example 29

1-[N-(2-Methoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

- 5 Phenyl N-(2-methoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl) thiocarbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.
yield : 55%

m.p. : 169-170°C

- 10 ¹H NMR(CDCl₃) δ : 2.10(2H,m), 2.89(4H,m), 3.30(4H,t), 3.77(6H,s), 3.98(3H,s), 4.20(4H,t), 6.05(3H,m), 7.37(1H,s), 8.25(1H,s)

Example 30

1-[N-(2-Methoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)aminothiocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

- 15 Phenyl N-(2-methoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl) thiocarbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.
yield : 53%

- 20 m.p. : 159-161°C

¹H NMR(CDCl₃) δ : 2.09(2H,m), 2.28(6H,s), 2.87(4H,m), 3.67(4H,t), 4.00(3H,s), 4.21(4H,t), 6.57(3H,m), 6.93(1H,s), 8.24(1H,s)

Example 31

- 25 1-[(2-Methoxy-5,6,7,8-tetrahydroquinolin-3-yl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-[(2-methoxy-5,6,7,8-tetrahydroquinolin-3-yl)thiocarbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.

- 30 yield : 56%

m.p. : 160-161°C

¹H NMR(CDCl₃) δ : 1.77(2H,m), 1.83(2H,m), 2.70(2H,t), 2.76(2H,t), 3.38(4H,t), 3.79(6H,s), 3.96(3H,s), 4.16(4H,t), 6.12(3H,m), 7.45(1H,s), 8.03(1H,s)

35

Example 32

- 31 -

1-[(2-Methoxy-5,6,7,8-tetrahydroquinolin-3-yl)aminothiocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

- Phenyl N-(2-methoxy-5,6,7,8-tetrahydroquinolin-3-yl)thiocarbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with
- 5 the example 22 to obtain the titled compound.

yield : 54%

m.p. : 200-201 °C

- ¹H NMR(CDCl₃) δ : 1.77(2H,m), 1.84(2H,m), 2.34(6H,s), 2.71(3H,t), 2.75(3H,t), 3.47(4H,t), 3.97(3H,s), 4.42(4H,t), 6.35(3H,m), 6.91(1H,s),
- 10 7.91(1H,s)

Example 33

1-[(5,6-Dimethyl-2-methylaminopyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

- 15 Phenyl N-(5,6-dimethyl-2-methylaminopyridin-3-yl)carbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 53%

m.p. : 150-151 °C

- 20 ¹H NMR(CDCl₃) δ : 2.29(3H,s), 2.48(3H,s), 3.29(4H,t), 3.45(3H,s), 3.77(6H,s), 3.79(4H,t), 6.10(3H,m), 7.40(1H,s)

Example 34

- 1-[(5,6-Dimethyl-2-methylaminopyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:
- 25

Phenyl N-(5,6-dimethyl-2-methylaminopyridin-3-yl)carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 52%

- 30 m.p. : 160-162 °C

¹H NMR(CDCl₃) δ : 2.30(9H,s), 2.48(3H,s), 3.31(4H,t), 3.46(3H,s), 3.78(4H,t), 6.60(3H,m), 7.41(1H,s)

Example 35

- 35 1-[(5-Ethyl-6-methyl-2-methylaminopyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

- 32 -

Phenyl N-(5-ethyl-6-methyl-2-methylaminopyridin-3-yl)carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 56%

5 m.p. : 143-145°C

¹H NMR(CDCl₃) δ : 1.22(3H,t), 2.28(6H,s), 2.52(3H,s), 2.72(2H,q), 3.29(4H,t), 3.45(3H,s), 3.78(4H,t), 6.59(3H,m), 7.41(1H,s)

Example 36

10 1-[(2-Methylamino-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(2-methylamino-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)carbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

15 yield : 49%

m.p. : 148-150°C

¹H NMR(CDCl₃) δ : 2.09(2H,m), 2.95(4H,m), 3.30(4H,t), 3.47(3H,s), 3.77(4H,t), 3.80(6H,s), 6.10(3H,m), 7.49(1H,s)

20 Example 37

1-[(2-Methylamino-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-(2-methylamino-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

25 yield : 48%

m.p. : 185-187°C

¹H NMR(CDCl₃) δ : 2.14(2H,m), 2.29(6H,s), 2.95(4H,m), 3.32(4H,t), 3.47(3H,s), 3.79(4H,t), 6.59(3H,m), 7.48(1H,s)

30

Example 38

1-[[5,6-Dimethyl-2-(4'-t-butoxycarbonylpiperazinyl)pyridin-3-yl]aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-[5,6-dimethyl-2-(4'-t-butoxycarbonylpiperazinyl)pyridin-3-yl]carbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

- 33 -

yield : 58%

m.p. : 74-75°C

¹H NMR(CDCl₃) δ : 1.46(9H,s), 2.20(3H,s), 2.21(3H,s), 2.90(4H,t),
3.20(4H,t), 3.55(4H,t), 3.65(4H,t), 3.98(3H,s), 6.02(3H,m), 8.20(1H,s)

5

Example 39

1-([5,6-Dimethyl-2-(4'-t-butoxycarbonylpiperazinyl)pyridin-3-yl]
aminocarbonyl)-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-[5,6-dimethyl-2-(4'-butoxycarbonylpiperazinyl)pyridin-3-yl]

10 carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the
same way with the example 1 to obtain the titled compound.

yield : 56%

m.p. : 155-156°C

¹H NMR(CDCl₃) δ : 1.48(9H,s), 2.22(3H,s), 2.29(6H,s), 2.35(3H,s),
15 2.95(4H,t), 3.25(4H,t), 3.57(4H,t), 3.67(4H,t), 6.59(3H,m), 8.21(1H,s)

Example 40

1-([5-Ethyl-6-methyl-2-(4'-t-butoxycarbonylpiperazinyl)pyridin-3-yl]
aminocarbonyl)-4-(3,5-dimethoxyphenyl)piperazine:

20 Phenyl N-[5-ethyl-6-methyl-2-(4'-t-butoxycarbonylpiperazinyl)
pyridin-3-yl]carbamate and 1-(3,5-dimethoxyphenyl)piperazine were
reacted by the same way with the example 1 to obtain the titled
compound.

yield : 52%

25 m.p. : 119-120°C

¹H NMR(CDCl₃) δ : 1.25(3H,t), 1.48(9H,s), 2.38(3H,s), 2.51(2H,q),
2.96(4H,t), 3.27(4H,t), 3.58(8H,m), 3.78(6H,s), 6.08(3H,m), 8.24(1H,s)

Example 41

30 1-([5-Ethyl-6-methyl-2-(4'-t-butoxycarbonylpiperazinyl)pyridin-3-yl]
aminocarbonyl)-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-[5-ethyl-6-methyl-2-(4'-t-butoxycarbonylpiperazinyl)
pyridin-3-yl]carbamate and 1-(3,5-dimethylphenyl)piperazine were
reacted by the same way with the example 1 to obtain the titled

35 compound.

yield : 50%

- 34 -

m.p. : 126-128°C

¹H NMR(CDCl₃) δ : 1.20(3H,t), 1.49(9H,s), 2.29(6H,s), 2.39(3H,s),
2.52(2H,q), 2.98(4H,t), 3.23(4H,t), 3.59(8H,m), 6.59(3H,m), 7.58(1H,s),
8.26(1H,s)

5

Example 42

1-[(5,6-Dimethyl-2-piperazinylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(5,6-Dimethyl-2-(4'-t-butoxycarbonylpiperazinyl)pyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine(0.218g, 0.4mmol) was dissolved in dichloromethane : nitromethane = 2 : 1(10ml) and anisole(0.26g, 2.4mmol) and aluminum chloride(0.3g, 2.4mmol) were added slowly thereto. The mixture was stirred at room temperature for 20min. Distilled water(50ml) was added into the mixture and the mixture was made basic with saturated NaHCO₃ and extracted with dichloromethane and then concentrated under the reduced pressure to remove the solvent. The concentrate was purified by column chromatography(methanol : dichloromethane = 8:1) to obtain the titled compound.

20 yield : 89%

m.p. : oil phase

¹H NMR(CDCl₃) δ : 2.21(3H,s), 2.35(3H,s), 3.02(4H,t), 3.34(4H,t),
3.59(4H,t), 3.62(4H,t), 3.78(6H,s), 6.08(3H,m), 8.18(1H,s)

25 Example 43

1-[(5,6-Dimethyl-2-piperazinylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[(5,6-Dimethyl-2-(4'-t-butoxycarbonylpiperazinyl)pyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 42 to obtain the titled compound.
yield : 85%

m.p. : 103-105°C

¹H NMR(CDCl₃) δ : 2.16(3H,s), 2.24(6H,s), 2.40(3H,s), 3.30(4H,t),
3.44(4H,t), 3.50(4H,t), 3.81(4H,t), 6.95(3H,m), 7.72(1H,s)

35

Example 44

- 35 -

1-[(5-Ethyl-6-methyl-2-piperazinylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(5-Ethyl-6-methyl-2-(4'-t-butoxycarbonylpiperazinyl)pyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 42 to obtain the titled compound.

yield : 88%

m.p. : 68-70°C

¹H NMR(CDCl₃) δ : 1.20(3H,t), 2.40(3H,s), 2.52(2H,q), 2.75(4H,t), 3.32(4H,t), 3.70(8H,m), 3.78(6H,s), 6.09(3H,m), 7.68(1H,s), 8.23(1H,s)

10

Example 45

1-[(5-Ethyl-6-methyl-2-piperazinylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[(5-Ethyl-6-methyl-2-(4'-t-butoxycarbonylpiperazinyl)pyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 42 to obtain the titled compound.

yield : 85%

m.p. : 100-102°C

¹H NMR(CDCl₃) δ : 1.20(3H,t), 2.28(6H,s), 2.39(3H,s), 2.65(2H,q), 2.76(4H,t), 3.00(4H,t), 3.23(4H,t), 3.70(4H,t), 6.58(3H,m), 7.66(1H,s), 8.24(1H,s)

20

Example 46

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)carbamate(200mg, 0.67mmol) and 1-(3,5-dimethoxyphenyl)piperazine(150mg, 0.67mmol) were dissolved in anhydrous tetrahydrofuran(15ml) and DBU(100mg, 0.67mmol) was added. The mixture was stirred at room temperature for 2 hrs and concentrated under the reduced pressure to remove tetrahydrofuran. The concentrate was purified by column chromatography(ethylacetate : hexane = 1:2) to obtain the titled compound.

yield : 83%

m.p. : 149-151°C

¹H NMR(CDCl₃) δ : 2.57(3H,s), 2.65(3H,s), 3.28(4H,t,J=4.65Hz), 3.70(4H,t,

35

J=4.65Hz), 3.79(6H,s), 4.06(3H,s), 6.09(1H,s), 6.14(2H,d), 6.94(1H,s), 8.87(1H,s)

Example 47

- 5 1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 46 to obtain the titled compound.

- 10 yield : 82%

m.p. : 66-69°C

¹H NMR(CDCl₃) δ : 2.31(6H,s), 2.57(3H,s), 2.65(3H,s), 3.08(4H,t), 3.30(4H,t), 4.10(3H,s), 6.71(2H,d), 6.94(1H,s), 8.89(1H,s)

- 15 Example 48

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-difluorophenyl)piperazine:

Phenyl N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(3,5-difluorophenyl)piperazine were reacted by the same way with the example 46 to obtain the titled compound.

- 20

yield : 77%

m.p. : 180-181°C

¹H NMR(CDCl₃) δ : 2.57(3H,s), 2.65(3H,s), 3.33(4H,t,J=5.0Hz), 3.74(4H,t,J=5.0Hz), 4.07(3H,s), 6.37(1H,s), 6.46(2H,d), 6.93(1H,s), 8.85(1H,s)

25

Example 49

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dichlorophenyl)piperazine:

Phenyl N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)carbamate and

- 30 1-(3,5-dichlorophenyl)piperazine were reacted by the same way with the example 46 to obtain the titled compound.

yield : 81%

m.p. : oil phase

- 35 ¹H NMR(CDCl₃) δ : 2.57(3H,s), 2.65(3H,s), 3.34(4H,t), 3.78(4H,t), 4.04(3H,s), 6.93(3H,m), 8.80(1H,s)

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Example 50

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2,3-dimethylphenyl)piperazine:

- Pheny N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)carbamate and
5 1-(2,3-dimethylphenyl)piperazine were reacted by the same way with the example 46 to obtain the titled compound.

yield : 81%

m.p. : 173-174°C

- ¹H NMR(CDCl₃) δ : 2.29(6H,s), 2.58(3H,s), 2.65(3H,s), 2.98(4H,t),
10 3.70(4H,t), 4.06(3H,s), 6.91(1H,d), 6.97(1H,s), 7.10(1H,t), 8.89(1H,s)

Example 51

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine:

- 15 Phenyl N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 46 to obtain the titled compound.

yield : 79%

m.p. : 153-154°C

- 20 ¹H NMR(CDCl₃) δ : 2.58(3H,s), 2.65(3H,s), 3.15(4H,t), 3.73(4H,t),
3.90(3H,s), 4.06(3H,s), 6.91(1H,d), 6.96(1H,d), 6.97(1H,s), 7.10(1H,t),
8.89(1H,s)

Example 52

- 25 1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3-hydroxyphenyl)piperazine:

Phenyl N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(3-hydroxyphenyl)piperazine were reacted by the same way with the example 46 to obtain the titled compound.

- 30 yield : 76%

m.p. : oil phase

¹H NMR(CDCl₃) δ : 2.60(3H,s), 2.72(3H,s), 3.34(4H,t), 3.79(4H,t),
3.98(3H,s), 6.45(3H,m), 6.98(1H,m), 8.97(1H,s)

- 35 Example 53

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminothiocabonyl]-4-(3,5

-dimethoxyphenyl)piperazine:

Phenyl N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)thiocarbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.

5 yield : 77%

m.p. : 167-169°C

¹H NMR(CDCl₃) δ : 2.58(3H,s), 2.68(3H,s), 3.47(4H,t), 3.81(6H,s), 4.05(3H,s), 4.36(4H,t), 6.42(3H,m), 7.49(1H,s), 9.05(1H,s)

10 Example 54

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminothiocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)thiocarbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with

15 the example 22 to obtain the titled compound.

yield : 75%

m.p. : 176-177°C

¹H NMR(CDCl₃) δ : 2.34(6H,s), 2.58(3H,s), 2.68(3H,s), 3.48(4H,t), 4.06(3H,s), 4.43(4H,t), 7.05(3H,m), 7.52(1H,s), 9.04(1H,s)

20

Example 55

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminothiocarbonyl]-4-(3-hydroxyphenyl)piperazine:

Phenyl N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)thiocarbamate and 25 1-(3-hydroxyphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.

yield : 71%

m.p. : 114-115°C

¹H NMR(CDCl₃) δ : 2.56(3H,s), 2.75(3H,s), 3.68(4H,t), 4.05(3H,s), 30 4.45(4H,t), 7.30(4H,m), 9.03(1H,s)

Mass(EI) m/z : Calcd for C₂₃H₃₀N₄O₄S₁ 458.1987, found 458.2527

Example 56

1-[(5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

35 1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-

- 39 -

dimethoxyphenyl)piperazine(100mg, 0.23mmol) was dissolved in anhydrous ethanol(15ml) and NaBH₄(8.66mg) was added. The reaction solution was stirred at room temperature for 2 hours. The mixture was concentrated under the reduced pressure to remove ethanol and purified by column chromatography (ethylacetate : hexane = 2:1) to obtain the titled compound.

yield : 97%

m.p. : 124-126°C

¹H NMR(CDCl₃) δ : 1.48(3H,d), 2.42(3H,s), 3.27(4H,t), 3.69(4H,t),
3.79(6H,s), 3.99(3H,s), 5.03(1H,q), 6.09(1H,s), 6.15(2H,d), 6.90(1H,s),
8.46(1H,s)

Mass(EI) m/z : Calcd for C₂₂H₃₀N₄O₅ 430.2216, found 430.2265

Example 57

1-([5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl)-4-(3,5-dimethylphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 56 to obtain the titled compound.

yield : 95%

m.p. : 153-154°C

¹H NMR(CDCl₃) δ : 1.48(3H,d), 2.30(6H,s), 2.42(3H,s), 3.26(4H,t),
3.68(4H,t), 3.99(3H,s), 5.05(1H,q), 6.71(2H,d), 6.96(1H,s), 8.46(1H,s)

Mass(EI) m/z : Calcd for C₂₂H₃₀N₄O₃ 398.2317, found 398.2343

Example 58

1-([5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl)-4-(2,3-dimethylphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2,3-dimethylphenyl)piperazine was reacted by the same way with the example 56 to obtain the titled compound.

yield : 96%

m.p. : 100-102°C

¹H NMR(CDCl₃) δ : 1.47(3H,d), 1.59(3H,s), 2.25(3H,s), 2.28(3H,s),
2.43(3H,s), 2.93(4H,t), 3.66(4H,t), 3.99(3H,s), 5.05(1H,q), 6.93(3H,m),
7.11(1H,m), 8.48(1H,s)

Example 59

1-([5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl)-4-(3,5-difluorophenyl)piperazine:

- 5 1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-difluorophenyl)piperazine was reacted by the same way with the example 56 to obtain the titled compound.

yield : 97%

m.p. : 184-186°C

- 10 ¹H NMR(CDCl₃) δ : 1.48(3H,d), 2.50(3H,s), 3.30(4H,t), 3.70(4H,t), 4.11(3H,s), 5.06(1H,q), 6.33(1H,s), 6.42(2H,d), 6.92(1H,s), 8.54(1H,s)

Example 60

1-([5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl)-4-(3,5-dichlorophenyl)piperazine:

- 15 1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dichlorophenyl)piperazine was reacted by the same way with the example 56 to obtain the titled compound.

yield : 95%

- 20 m.p. : 197-200°C

¹H NMR(CDCl₃) δ : 1.46(3H,d), 2.41(3H,s), 3.28(4H,t), 3.66(4H,t), 3.96(3H,s), 5.20(1H,q), 7.02(3H,m), 8.42(1H,s)

Example 61

- 25 1-([5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl)-4-(2-methoxyphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine was reacted by the same way with the example 56 to obtain the titled compound.

- 30 yield : 97%

m.p. : 88-90°C

¹H NMR(CDCl₃) δ : 1.47(3H,d), 2.42(3H,s), 3.11(4H,t), 3.70(4H,t), 3.89(3H,s), 3.99(3H,s), 5.03(1H,q), 6.89(3H,m), 6.94(1H,s), 7.05(1H,m), 8.48(1H,s)

35

Example 62

- 41 -

1-([5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl)-4-(3-hydroxyphenyl)piperazine:

1-[5-Acetyl-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl]-4-(3-hydroxyphenyl)piperazine was reacted by the same way with the example 56 to obtain the titled compound.

yield : 87%

m.p. : 194-196°C

¹H NMR(CDCl₃) δ : 1.47(3H,d), 2.41(3H,s), 3.27(4H,t), 3.79(4H,t), 3.98(3H,s), 5.04(1H,q), 6.57(3H,m), 6.90(1H,s), 7.13(1H,t), 8.41(1H,s)

10

Example 63

1-([5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminothiocarbonyl)-4-(3,5-dimethoxyphenyl)piperazine:

1-[5-Acetyl-2-methoxy-6-methylpyridin-3-yl]aminothiocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 56 to obtain the titled compound.

yield : 89%

m.p. : 189-190°C

¹H NMR(CDCl₃) δ : 1.47(3H,d), 2.43(3H,s), 3.35(4H,t), 3.78(6H,s), 3.97(3H,s), 4.09(4H,t), 5.05(1H,q), 6.07(3H,m), 7.35(1H,s), 8.42(1H,s)

20

Example 64

1-([5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminothiocarbonyl)-4-(3,5-dimethylphenyl)piperazine:

1-[5-Acetyl-2-methoxy-6-methylpyridin-3-yl]aminothiocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 56 to obtain the titled compound.

yield : 88%

m.p. : 170-172°C

¹H NMR(CDCl₃) δ : 1.46(3H,d), 2.29(6H,s), 2.43(3H,s), 3.43(4H,t), 3.97(3H,s), 4.10(4H,t), 5.06(1H,q), 6.60(3H,m), 7.37(1H,s), 8.40(1H,s)

30

Example 65

1-([5-(1-Hydroxy-1-methylethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl)-4-(3,5-dimethoxyphenyl)piperazine:

35

1-[5-Acetyl-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl]-4-(3,5-

- 42 -

dimethoxyphenyl)piperazine(214mg, 0.50mmol) was dissolved in tetrahydrofuran(10ml) and CH_3MgBr (0.50ml, 1.50mmol) was added slowly. The mixture solution was refluxed for 15 hrs and concentrated under the reduced pressure to remove the solvent and extracted with ethylacetate, dried and filtered. The resultant was purified by column chromatography(ethylacetate : hexane = 1: 2) to obtain the titled compound.

yield : 84%

m.p. : 146-148°C

^1H NMR(CDCl_3) δ : 1.64(6H,s), 2.64(3H,s), 3.25(4H,t), 3.67(4H,t), 3.78(6H,s), 3.99(3H,s), 6.07(3H,m), 6.86(1H,s), 8.47(1H,s)

Example 66

1-([5-(1-Hydroxy-1-methylethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl)-4-(3,5-dimethylphenyl)piperazine:
1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 65 to obtain the titled compound.
yield : 81%

m.p. : oil phase

^1H NMR(CDCl_3) δ : 1.64(6H,s), 2.29(6H,s), 2.65(3H,s), 3.24(4H,t), 3.67(4H,t), 3.99(3H,s), 6.59(3H,m), 7.05(1H,s), 8.48(1H,s)

Example 67

1-([5-(1-Hydroxy-1-methylpropyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl)-4-(3,5-dimethoxyphenyl)piperazine:
1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine(214mg, 0.50mmol) was dissolved in tetrahydrofuran(10ml) and $\text{C}_2\text{H}_5\text{MgBr}$ (0.50mg, 1.50mmol) was added slowly. The mixture solution was refluxed for 15 hours and concentrated under the reduced pressure to remove the solvent and extracted with ethylacetate, dried and filtered. The resultant was purified by column chromatography(ethylacetate : hexane = 1:2) to obtain the titled compound.

yield : 76%

m.p. : 127-129°C

¹H NMR(CDCl₃) δ : 0.83(3H,t), 1.63(3H,s), 1.94(2H,m), 2.61(3H,s),
3.26(4H,t), 3.68(4H,t), 3.79(6H,s), 3.99(3H,s), 6.08(3H,m), 6.86(1H,s),
8.44(1H,s)

5 Example 68

1-([5-(1-Hydroxy-1-methylpropyl)-2-methoxy-6-methylpyridin-3-yl]
aminocarbonyl)-4-(3,5-dimethylphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-
dimethylphenyl)piperazine was reacted by the same way with the
10 example 67 to obtain the titled compound.

yield : 74%

m.p. : 164-165°C

¹H NMR(CDCl₃) δ : 0.83(3H,t), 1.60(3H,s), 1.95(2H,m), 2.29(6H,s),
2.61(3H,s), 3.23(4H,t), 3.67(4H,t), 3.99(3H,s), 6.59(3H,m), 6.87(1H,s),
15 8.45(1H,s)

Example 69

1-[5-([4-(3,5-Dimethoxyphenyl)piperazino]carbonyl)amino]-6-methoxy-2-
methylpyridin-3-yl]ethyl ethanthioate:

20 Triphenylphosphine(262mg, 1.0mmol) was dissolved in
tetrahydrofuran(15ml) and diethyl azodicarboxylate(157μl, 1.0mmol) was
added and then the mixture was stirred at 0°C for 30min.

1-([5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl)-
4-(3,5-dimethoxyphenyl)piperazine(213mg, 0.5mmol) and thioacetic
25 acid(72μl, 1.0mmol) were dissolved in tetrahydrofuran and was added
into the above solution. The mixture solution was stirred at 0°C for
1hour and at room temperature for 1hour and then was concentrated
under the reduced pressure to remove the solvent. The concentrate was
purified by column chromatography(ethylacetate : hexane = 1:2) to

30 obtain the titled compound.

yield : 62%

m.p. : oil phase

¹H NMR(CDCl₃) δ : 1.55(3H,d), 2.20(3H,s), 2.39(3H,s), 3.15(4H,t),
3.57(4H,t), 3.69(6H,s), 3.90(3H,s), 4.74(1H,q), 6.01(3H,m), 6.89(1H,s),
35 8.33(1H,s)

Example 70

1-[5-([4-(3,5-Dimethylphenyl)piperazino]carbonyl)amino)-6-methoxy-2-methylpyridin-3-yl]ethyl ethanthioate:

- 1-([5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl)-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 69 to obtain the titled compound.

yield : 60%

m.p. : oil phase

- ¹H NMR(CDCl₃) δ : 1.60(3H,d), 2.26(6H,s), 2.52(3H,s), 3.20(4H,t),
3.64(4H,t), 3.96(3H,s), 4.80(1H,q), 6.56(3H,m), 6.91(1H,s), 8.38(1H,s)

Example 71

1-([2-Methoxy-6-methyl-5-(1-sulfanylmethyl)]aminocarbonyl)-4-(3,5-dimethoxyphenyl)piperazine:

- 1-[5-([4-(3,5-Dimethoxyphenyl)piperazino]carbonyl)amino)-6-methoxy-2-methylpyridin-3-yl]ethyl ethanthioate(180mg, 0.37mmol) was dissolved in tetrahydrofuran(15ml) and LiAlH₄(15mg, 0.4mmol) was added and then the mixture was stirred at 0°C for 20min. 2N-HCl was added the above solution. The mixture was concentrated under the reduced pressure to remove the solvent and extracted with dichloromethane, dried and filtered. The resultant was concentrated under the reduced pressure and purified by column chromatography(ethylacetate : hexane = 1:2) to obtain the titled compound.

yield : 88%

- m.p. : oil phase

¹H NMR(CDCl₃) δ : 1.42(3H,d), 2.39(3H,s), 3.25(4H,t), 3.66(4H,t), 3.76(6H,s), 3.96(3H,s), 5.02(1H,q), 6.17(3H,m), 6.87(1H,s), 8.41(1H,s)

Example 72

- 1-([2-Methoxy-6-methyl-5-(1-sulfanylmethyl)]aminocarbonyl)-4-(3,5-dimethylphenyl)piperazine:

1-[5-([4-(3,5-Dimethylphenyl)piperazino]carbonyl)amino)-6-methoxy-2-methylpyridin-3-yl]ethyl ethanthioate was reacted by the same way with the example 71 to obtain the titled compound.

- yield : 87%

m.p. : oil phase

^1H NMR(CDCl_3) δ : 1.43(3H,d), 2.28(6H,s), 2.40(3H,s), 3.25(4H,t), 3.72(4H,t), 5.03(1H,q), 6.64(3H,m), 6.88(1H,s), 8.42(1H,s)

Exmaple 73

- 5 1-[(2-Methoxy-6-methyl-5-vinylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
1-[[5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine was dissolved in chloroform(15ml) and pyridinium p-toluensulfonate(60mg, 0.23mmol) was added and then
10 the mixture solution was refluxed 16hours. The above solution was concentrated under the reduced pressure to remove chloroform and purified by column chromatography to obtain the titled compound.
yield : 93%
m.p. : 140-141°C
- 15 ^1H NMR(CDCl_3) δ : 2.43(3H,s), 3.27(4H,t), 3.69(4H,t), 3.79(6H,s), 4.00(3H,s), 5.25(1H,d), 5.65(1H,d), 6.08(1H,s), 6.13(2H,d), 6.82(1H,d), 6.91(1H,s), 8.53(1H,s)
Mass(EI) m/z : Calcd for $\text{C}_{22}\text{H}_{28}\text{N}_4\text{O}_4$ 412.2110, found 412.2119

20 Example 74

- 1-[(2-Methoxy-6-methyl-5-vinylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:
1-[[5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with
25 the example 73 to obtain the titled compound.
yield : 94%
m.p. : 131-132°C
- ^1H NMR(CDCl_3) δ : 1.57(3H,s), 2.31(6H,s), 2.43(1H,s), 3.25(4H,t), 3.68(4H,t), 4.00(3H,s), 5.25(1H,d), 5.65(1H,d) 6.60(3H,m), 6.82(1H,dd),
30 6.92(1H,s), 8.53(1H,s)
Mass(EI) m/z : Calcd for $\text{C}_{22}\text{H}_{28}\text{N}_4\text{O}_2$ 380.2212, found 380.2236

Example 75

- 1-[(2-Methoxy-6-methyl-5-vinylpyridin-3-yl)aminocarbonyl]-4-(3,5-difluorophenyl)piperazine:
35 1-[[5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl]

-4-(3,5-difluorophenyl)piperazine was reacted by the same way with the example 73 to obtain the titled compound.

yield : 93%

m.p. : 160-161°C

5 ¹H NMR(CDCl₃) δ : 2.44(3H,s), 3.30(4H,t,J=5.5Hz), 3.68(4H,t,J=5.5Hz), 4.01(3H,s), 5.26(1H,d), 5.65(1H,d), 6.30(1H,s), 6.39(2H,d), 6.81(1H,dd), 8.53(1H,s)

Mass(EI) m/z : Calcd for C₂₂H₂₈N₄O₄ 412.2110, found 412.2102

10 Example 76

1-[(5-Isopropenyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

-{[5-(1-Hydroxy-1-methylethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl}-4-(3,5-dimethoxyphenyl)piperazine was reacted by the
15 same way with the example 73 to obtain the titled compound.

yield : 96%

m.p. : 83-85°C

¹H NMR(CDCl₃) δ : 2.01(3H,s), 2.38(3H,s), 3.25(4H,t), 3.66(4H,t),
3.78(6H,s), 3.99(3H,s), 4.86(1H,s), 5.30(1H,s), 6.11(3H,m), 6.90(1H,s),
20 8.18(1H,s)

Example 77

1-[(5-Isopropenyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

25 1-{[5-(1-Hydroxy-1-methylethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl}-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with example 73 to obtain the titled compound.
yield : 93%

m.p. : 140-142°C

30 ¹H NMR(CDCl₃) δ : 2.01(3H,s), 2.29(6H,s), 2.28(3H,s), 3.23(4H,t), 3.66(4H,t), 3.99(3H,s), 4.86(1H,s), 5.18(1H,s), 6.59(3H,m), 6.91(1H,s), 8.18(1H,s)

Example 78

35 Ethyl 2-{1-[5-({[4-(3,5-dimethoxyphenyl)piperazino]carbonyl)amino]-6-methoxy-2-methylpyridin-3-yl]ethoxy}acetate:

- 47 -

- 1-([5-(1-Hydroxy)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl)-4-(3,5-dimethoxyphenyl)piperazine(0.5mmol) was dissolved in dimethylformamide(15ml) and NaH(18.5mg, 0.5mmol) was added and then the mixture solution was stirred at room temperature for 15min.
- 5 Ethylbromoacetate(83.5mg, 0.5mmol) was added into the above mixture and stirred at room temperature for 3hours. The mixture was concentrated under the reduced pressure to remove the solvent and purified by column chromatography(ethylacetate : hexane = 1:2) to obtain the titled compound.
- 10 yield : 89%
m.p. : oil phase
¹H NMR(CDCl₃) δ : 1.25(3H,t), 1.34(3H,d), 2.42(3H,s), 3.00(4H,t), 3.29(4H,t), 3.74(6H,s), 3.97(3H,s), 4.16(4H,s), 4.53(1H,q), 6.03(3H,m), 7.58(1H,s)

15

Example 79

- 4-(1-[5-([4-(3,5-Dimethoxyphenyl)piperazino]carbonyl)amino)-6-methoxy-2-methylpyridin-3-yl]ethoxy)-4-oxobutanoic acid:
1-([5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl)-4-(3,5-dimethoxyphenyl)piperazine(107mg, 0.25mmol) and dimethylaminopyridine(3mg, 0.025mmol) were dissolved in pyridine and anhydrous succinic acid(50mg, 0.5mmol) was added. The mixture was stirred at room temperature for 5hrs. Distilled water was added into the above mixture. The above solution was extracted with CH₂Cl₂ and the organic phase washed with 1N-HCl and then concentrated under the reduced pressure to remove the solvent. The concentrate was purified by column chromatography(dichloromethane : methanol = 20:1) to obtain the titled compound.
- 25 yield : 78%
m.p. : 158-160°C
¹H NMR(CDCl₃) δ : 1.42(3H,d), 2.43(3H,s), 2.61(4H,m), 3.24(4H,t), 3.66(4H,t), 3.76(6H,s), 3.95(3H,s), 5.94(1H,q), 6.04(3H,m), 6.89(1H,s), 8.13(1H,s)

30

35

Example 80

4-(1-[5-([4-(3,5-Dimethylphenyl)piperazino]carbonyl)amino)-6-methoxy-

- 48 -

2-methylpyridin-3-yl]ethoxy)-4-oxobutanoic acid:

1-[[5-(1-hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 79 to obtain the titled compound.

5 yield : 76%

m.p. : 138-140°C

¹H NMR(CDCl₃) δ : 1.43(3H,d), 2.27(6H,s), 2.55(3H,s), 2.65(4H,m), 3.24(4H,t), 3.69(4H,t), 3.95(3H,s), 5.95(1H,q), 6.60(3H,m), 6.88(1H,s), 8.11(1H,s)

10

Example 81

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

15 a) Phenyl N-(2-methoxyquinolin-3-yl)carbamate:

3-Amino-2-methoxyquinoline(4g, 23mmol) and phenyl chloroformate(4.04g, 25mmol) were dissolved in dichloromethane and stirred at room temperature for 2 hours. The above mixture was concentrated under the reduced pressure to remove dichloromethane and purified by column chromatography(hexane : ether =8:1) to obtain the

20 titled compound.

yield : 75%

m.p. : oil phase

¹H NMR (CDCl₃): δ 4.01(3H,s), 7.30(5H,s), 7.41(1H,t), 7.70(1H,d), 7.71(1H,d), 8.71(1H,s)

25

b) 1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)carbamate(148mg, 0.5mmol) and 1-(3,5-dimethoxyphenyl)piperazine(112mg, 0.5mmol) were dissolved in anhydrous tetrahydrofuran and DBU(117mg, 0.75mmol) was added. The solution was stirred at room temperature for 2 hours. The mixture was concentrated under the reduced pressure to remove tetrahydrofuran and purified by column chromatography(hexane : ether = 5:1) to obtain the

35

yield : 81%

- 49 -

m.p. : 200-201°C

¹H NMR (CDCl₃): δ 3.31(4H,t,J=5.0Hz), 3.74(4H,t), 3.79(6H,s), 4.17(3H,s), 6.09(1H,s), 6.17(2H,s), 7.35(1H,t), 7.49(1H,t), 7.71(1H,d), 7.78(1H,d), 8.78(1H,s)

5 Mass(EI) m/z : Calcd for C₂₃H₂₆N₄O₄ 422.1954, found 422.1952

Example 82

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl) piperazine:

10 Phenyl N-(2-methoxyquinolin-3-yl)carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.
yield : 79%

m.p. : 143-145°C

15 ¹H NMR (CDCl₃): δ 2.30(6H,s), 3.29(4H,t), 3.80(4H,t), 4.18(3H,s), 6.62(3H,m), 7.36(1H,t), 7.49(1H,t), 7.71(1H,d), 7.78(1H,d), 8.79(1H,s)

Mass(EI) m/z : Calcd for C₂₃H₂₆N₄O₂ 390.2055, found 390.2066

Example 83

20 1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(2,3-dimethylphenyl) piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)carbamate and 1-(2,3-dimethylphenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

25 yield : 83%

m.p. : 174-175°C

¹H NMR (CDCl₃): δ 2.20(3H,s), 2.39(3H,s), 3.28(4H,t), 3.69(4H,t), 3.93(3H,s), 5.98(1H,s), 6.30(1H,t), 6.37(1H,s), 6.39(1H,s), 6.63(1H,s)

30 Example 84

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-difluorophenyl) piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)carbamate and 1-(3,5-difluorophenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

35 yield : 78%

m.p. : 158-159°C

¹H NMR (CDCl₃): δ 3.32(4H,t,J=5.0Hz), 3.72(4H,t,J=5.0Hz), 4.19(3H,s), 6.29(1H,s), 6.39(2H,d), 7.36(1H,t), 7.50(1H,t), 7.71(1H,d), 7.81(1H,d), 8.78(1H,s)

5

Example 85

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dichlorophenyl) piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)carbamate and

10 1-(3,5-dichlorophenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

yield : 56%

m.p. : 156-158°C

¹H NMR (CDCl₃): δ 3.33(4H,t), 3.73(4H,t), 4.21(3H,s) 6.79(1H,s),
15 6.83(1H,d), 6.93(1H,t), 7.26(1H,t), 7.38(1H,t), 7.52(1H,t), 7.71(1H,d), 7.83(1H,d)

Mass(EI) m/z : Calcd for C₂₁H₂₀N₄O₂Cl₂ 430.0963, found 430.0977

Example 86

20 1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(2-fluorophenyl)piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)carbamate and

1-(2-fluorophenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

yield : 81%

25 m.p. : 156-158°C

¹H NMR (CDCl₃): δ 3.18(4H,t), 3.74(4H,t), 4.18(3H,s), 6.99(2H,q), 7.07(2H,m), 7.35(2H,m), 7.50(1H,t), 7.70(1H,d), 7.77(1H,d)

Example 87

30 1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(2-chlorophenyl)piperazine:

Phenyl N-(2-methoxyquinoline-3-yl)carbamate and

1-(2-chlorophenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

yield : 78%

35 m.p. : 79-80°C

¹H NMR (CDCl₃): δ 3.32(4H,t), 3.74(4H,t), 4.20(3H,s), 6.82(2H,q),

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6.94(2H,m), 7.34(2H,m), 7.48(1H,d), 7.70(1H,d), 7.78(1H,d)

Example 88

- 1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3-chlorophenyl)piperazine:
5 Phenyl N-(2-methoxyquinolin-3-yl)carbamate and
1-(3-chlorophenyl)piperazine were reacted by the same way with the
example 81 to obtain the titled compound.

yield : 73%

m.p. : 97-98°C

- 10 ¹H NMR (CDCl₃): δ 3.31(4H,t), 3.73(4H,t), 4.18(3H,s), 6.82(1H,d),
6.87(1H,d), 6.92(1H,s), 7.21(1H,t), 7.32(1H,s), 7.37(1H,t), 7.51(1H,t),
7.70(1H,d), 7.78(1H,d), 8.80(1H,s)

Example 89

- 15 1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3-hydroxyphenyl)
piperazine:
Phenyl N-(2-methoxyquinolin-3-yl)carbamate and
1-(3-hydroxyphenyl)piperazine were reacted by the same way with the
example 81 to obtain the titled compound.

- 20 yield : 75%

m.p. : 190-191 °C

¹H NMR (CDCl₃): δ 3.33(4H,t), 3.80(4H,t), 4.19(3H,s), 6.47(1H,s),
6.62(2H,s), 7.16(1H,t), 7.32(1H,s), 7.37(1H,t), 7.51(1H,t), 7.72(1H,d),
7.78(1H,d), 8.78(1H,s)

25

Example 90

- 1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)
piperazine:
Phenyl N-(2-methoxyquinolin-3-yl)carbamate and
30 1-(2-methoxyphenyl)piperazine were reacted by the same way with the
example 81 to obtain the titled compound.

yield : 88%

m.p. : 159-161 °C

- 35 ¹H NMR (CDCl₃): δ 3.28(4H,t), 3.71(4H,t), 3.81(3H,s), 4.18(3H,s),
6.52(2H,s), 6.62(1H,s), 7.23(1H,t), 7.31-7.53(3H,m), 7.72(2H,m), 8.81(1H,s)

Example 91

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(2-methylthiophenyl)
piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)carbamate and

- 5 1-(2-methylthiophenyl)piperazine were reacted by the same way with
the example 81 to obtain the titled compound.

yield : 78%

m.p. : 147-149°C

- ¹H NMR (CDCl₃): δ 2.44(3H,s), 3.07(4H,t), 3.75(4H,t), 4.18(3H,s),
10 7.13(3H,m), 7.18(1H,d), 7.39(2H,m), 7.70(3H,m), 8.81(1H,s)

Example 92

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3-isopropoxyphenyl)
piperazine:

- 15 Phenyl N-(2-methoxyquinolin-3-yl)carbamate and
1-(3-isopropoxyphenyl)piperazine were reacted by the same way with
the example 81 to obtain the titled compound.

yield : 93%

m.p. : 111-113°C

- 20 ¹H NMR (CDCl₃): δ 1.34(6H,d), 3.30(4H,t), 3.74(4H,t), 4.18(3H,s),
4.55(1H,m), 6.49(2H,s), 7.05(1H,s), 7.20(1H,t), 7.32(1H,s), 7.37(1H,t),
7.50(1H,t), 7.70(1H,d), 7.77(1H,d), 8.80(1H,s)

Example 93

- 25 1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3-cyclopropylmethoxy
phenyl)piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)carbamate and

1-(3-cyclopropylmethoxyphenyl)piperazine were reacted by the same
way with the example 81 to obtain the titled compound.

- 30 yield : 90%

m.p. : 146-147°C

- ¹H NMR (CDCl₃): δ 0.36(2H,t), 0.65(2H,m), 1.28(1H,m), 3.31(4H,t),
3.75(4H,t), 3.80(2H,d), 4.18(3H,s), 6.50(1H,s), 6.60(2H,s), 7.19(1H,t),
7.32(1H,s), 7.37(1H,t), 7.50(1H,t), 7.70(1H,d), 7.77(1H,d), 8.79(1H,s)

35

Example 94

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1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(2-methoxy-5-methylphenyl)piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)carbamate and

1-(2-methoxy-5-methylphenyl)piperazine were reacted by the same way

5 with the example 81 to obtain the titled compound.

yield : 76%

m.p. : 115-116°C

¹H NMR (CDCl₃): δ 2.30(3H,s), 3.14(4H,t), 3.75(4H,t), 3.87(3H,s),
4.18(3H,s), 6.79(2H,m), 6.84(1H,d), 7.35(2H,m), 7.50(1H,t), 7.72(1H,d),

10 7.77(1H,d), 8.82(1H,s)

Example 95

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(2-methoxy-5-phenylphenyl)piperazine:

15 Phenyl N-(2-methoxyquinolin-3-yl)carbamate and

1-(2-methoxy-5-phenylphenyl)piperazine were reacted by the same way
with the example 81 to obtain the titled compound.

yield : 77%

m.p. : 122-123°C

20 ¹H NMR (CDCl₃): δ 3.38(4H,t) 3.86(4H,t), 3.97(3H,s), 4.18(3H,s),
7.05(2H,m), 7.34-7.45(6H,m), 7.50(1H,t), 7.56(2H,d), 7.71(2H,d),
7.78(2H,d), 8.88(1H,s)

Example 96

25 1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(5-methoxy-2-methylphenyl)piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)carbamate and

1-(5-methoxy-2-methylphenyl)piperazine were reacted by the same way
with the example 81 to obtain the titled compound.

30 yield : 82%

m.p. : 128-130°C

¹H NMR (CDCl₃): δ 2.30(3H,s), 3.37(4H,t), 3.84(4H,t), 3.78(3H,s),
3.97(3H,s), 7.05(2H,m), 7.13(1H,d), 7.38(3H,m), 7.62(1H,d), 7.80(1H,s),
8.88(1H,s)

35

Example 97

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(1-naphthyl)piperazine:
Phenyl N-(2-methoxyquinolin-3-yl)carbamate and
1-(1-naphthyl)piperazine were reacted by the same way with the
example 81 to obtain the titled compound.

5 yield : 68%

m.p. : 158-160°C

¹H NMR (CDCl₃): δ 3.22(4H,t), 3.86(4H,t), 4.20(3H,s), 7.13(1H,d),
7.38(2H,m), 7.43(1H,t), 7.53(3H,m), 7.62(1H,d), 7.72(1H,d), 7.80(1H,d),
7.86(1H,d), 8.24(1H,d), 8.84(1H,s)

10

Example 98

1-[N-(2-Methoxyquinolin-3-yl)-N-methylaminocarbonyl]-4-(3,5-
dimethoxyphenyl)piperazine:

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)
15 piperazine(106mg, 0.25mmol) was dissolved in dimethylformamide(15ml)
and sodium hydride(6.0mg, 0.25mmol) was added and the solution was
stirred at room temperature for 15 min. Iodomethane(35mg, 0.25mmol)
was added to the above solution. The mixture was stirred at room
temperature for 16 hours and concentrated under the reduced pressure
20 to remove dimethylformamide. The concentrate was purified by column
chromatography(ethylacetate : hexane = 1:2) to obtain the titled
compound.

yield : 93%

m.p. : 88-89°C

25 ¹H NMR (CDCl₃): δ 2.93(4H,t), 3.17(3H,s), 3.34(4H,t), 3.72(6H,s),
4.15(3H,t), 5.95(2H,s), 5.98(1H,s), 7.40(1H,t), 7.61(2H,m), 7.73(1H,s),
7.84(1H,d)

Mass(EI) m/z : Calcd for C₂₄H₂₈N₄O₄ 436.2110, found 436.2105

30 Example 99

1-[N-Ethyl-N-(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethox
yphenyl)piperazine:

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)
piperazine(106mg, 0.25mmol) was dissolved in dimethylformamide(15ml)
35 and was sodium hydride(6.0mg, 0.25mmol) was added and the solution
was stirred at room temperature for 15 min. Iodoethane(35mg,

- 55 -

0.25mmol) was added to the above solution. The mixture was stirred at room temperature for 16 hours and concentrated under the reduced pressure to remove dimethylformamide. The concentrate was purified by column chromatography(ethylacetate : hexane = 1:2) to obtain the titled compound.

yield : 91%

m.p. : 118-120°C

¹H NMR (CDCl₃): δ 1.16(3H,t), 2.89(4H,t), 3.30(4H,t), 3.63(2H,m), 3.71(6H,s), 4.13(3H,s), 5.93(2H,s), 5.98(1H,s), 7.41(1H,t), 7.60(1H,t), 7.66(1H,d), 7.71(1H,s), 7.84(1H,d)

Mass(EI) m/z : Calcd for C₂₅H₃₀N₄O₄ 450.2227, found 450.2206

Example 100

1-[N-Isopropyl-N-(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)phenyl:

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine(106mg, 0.25mmol) was dissolved in dimethylformamide(15ml) and sodium hydride(6.0mg, 0.25mmol) was added and the reaction solution was stirred at room temperature for 15 min.

2-Propyliodide(42mg, 0.25mmol) was added to the above solution. The mixture was stirred at room temperature for 16 hours and concentrated under the reduced pressure to remove the dimethylformamide. The concentrate was purified by column chromatography(ethylacetate : hexane = 1:2) to obtain the titled compound.

yield : 87%

m.p. : 123-125°C

¹H NMR (CDCl₃): δ 1.21(6H,d), 2.79(4H,t), 3.29(4H,t), 3.70(6H,s), 4.08(3H,s), 4.41(1H,m), 5.90(2H,s), 5.96(1H,s), 7.43(1H,t), 7.63(1H,t), 7.69(1H,d), 7.75(1H,s), 7.83(1H,d)

30

Example 101

1-[N-Cyclopropylmethyl-N-(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine(106mg, 0.25mmol) was dissolved in dimethylformamide(15ml) and sodium hydride(6.2mg, 0.26mmol) was added and the solution was

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stirred at room temperature for 15 min. Bromomethylcyclopropane(22mg, 0.26mmol) was added to the above solution. The mixture was stirred at room temperature for 16 hours and concentrated under the reduced pressure to remove dimethylformamide. The concentrate was purified by column chromatography(ethylacetate : hexane = 1:2) to obtain the titled compound.

yield : 78%

m.p. : 118-120°C

¹H NMR (CDCl₃): δ 0.41(2H,m), 0.85(2H,m), 1.28(1H,m), 2.88(4H,t), 3.24(4H,t), 3.42(2H,d), 3.71(6H,s), 4.13(3H,s), 5.94(3H,s), 7.44(1H,d), 7.62(1H,d), 7.78(3H,m)

Example 102

1-[N-Benzyl-N-(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine(114mg, 0.27mmol) was dissolved in dimethylformamide(15ml) and sodium hydride(6.6mg, 0.27mmol) was added and the solution was stirred at room temperature for 15 min. Benzylbromide(46mg, 0.27mmol) was added to the above solution. The mixture was stirred at room temperature for 16 hours and concentrated under the reduced pressure to remove dimethylformamide. The concentrate was purified by column chromatography(ethylacetate : hexane = 1:2) to obtain the titled compound.

yield : 90%

m.p. : oil phase

¹H NMR (CDCl₃): δ 2.92(4H,t), 3.39(4H,t), 3.72(6H,s), 4.13(3H,s), 4.79(2H,s), 6.01(3H,m), 7.21(1H,m), 7.25(2H,m), 7.33(3H,m), 7.51(1H,s), 7.57(2H,m), 7.81(2H,d)

Example 103

1-[N-(2-Methoxyquinolin-3-yl)-N-methylaminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 98 to obtain the titled compound.

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yield : 92%

m.p : 142-143°C

¹H NMR (CDCl₃): δ 2.27(6H,d), 2.90(4H,t), 3.17(3H,s), 3.34(4H,t),
4.15(3H,s), 6.41(2H,s), 6.49(1H,s), 7.40(1H,t), 7.63(1H,t), 7.65(1H,d),
5 7.73(1H,s), 7.84(1H,d)

Mass(EI) m/z : Calcd for C₂₄H₂₈N₄O₂ 404.2212, found 404.2225

Example 104

1-[N-Ethyl-N-(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethyl
10 phenyl)piperazine:

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)
piperazine was reacted by the same way with the example 99 to obtain
the titled compound.

yield : 89%

15 m.p. : 84-86°C

¹H NMR (CDCl₃): δ 1.16(3H,t), 2.21(6H,s), 2.87(4H,t), 3.30(4H,t),
3.64(2H,q), 4.13(3H,t), 6.40(2H,s), 6.48(1H,s), 7.40(1H,t), 7.62(1H,t),
7.66(1H,d), 7.71(1H,s), 7.84(1H,d)

20 Example 105

1-[N-Isopropyl-N-(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-
dimethylphenyl)piperazine:

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)
piperazine was reacted by the same way with the example 100 to
25 obtain the titled compound.

yield : 84%

m.p. : 114-115°C

¹H NMR (CDCl₃): δ 1.21(6H,d), 2.20(6H,s), 2.77(4H,t), 3.28(4H,t),
4.08(3H,s), 4.39(1H,m), 6.37(2H,s), 6.46(1H,s), 7.41(1H,t), 7.63(1H,t),
30 7.69(1H,d), 7.75(1H,s), 7.83(1H,d)

Example 106

1-[N-Benzyl-N-(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-
dimethylphenyl)piperazine:

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)
piperazine was reacted by the same way with the example 102 to
35

obtain the titled compound.

yield : 90%

m.p. : oil phase

¹H NMR (CDCl₃): δ 2.24(6H,s), 2.87(4H,t), 3.31(4H,t), 4.13(3H,s),

5 4.80(2H,s), 6.42(3H,s), 7.49(1H,t), 7.62(2H,m), 7.72(2H,m)

Example 107

1-[N-(2-Methoxyquinolin-3-yl)-N-methylaminocarbonyl]-4-(3-isopropoxyphenyl)piperazine:

10 1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3-isopropoxyphenyl)piperazine was reacted by the same way with the example 98 to obtain the titled compound.

yield : 92%

m.p. : oil phase

15 ¹H NMR (CDCl₃): δ 1.28(6H,d), 2.97(4H,t), 3.18(3H,s), 3.37(4H,t), 4.14(3H,s), 4.49(1H,m), 6.41(3H,m), 7.13(1H,m), 7.40(1H,t), 7.62(1H,t), 7.66(1H,d), 7.74(1H,s), 7.84(1H,d).

Example 108

20 1-[N-Ethyl-N-(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3-isopropoxyphenyl)piperazine:

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3-isopropoxyphenyl)piperazine was reacted by the same way with the example 99 to obtain the titled compound.

25 yield : 87%

m.p. : oil phase

¹H NMR (CDCl₃): δ 1.16(3H,t), 1.34(6H,d), 2.89(4H,t), 3.30(4H,t), 3.63(2H,m), 4.13(3H,s), 4.55(1H,m), 6.49(2H,s), 7.05(1H,s), 7.20(1H,t), 7.32(1H,s), 7.37(1H,t), 7.50(1H,t), 7.70(1H,d), 7.77(1H,d), 8.80(1H,s)

30

Example 109

1-[(2-Methoxyquinolin-3-yl)aminothiocabonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)thiocarbamate(56mg, 0.5mmol) and
35 1-(3,5-dimethoxyphenyl)piperazine(111mg, 0.5mmol) were dissolved in anhydrous tetrahydrofuran and DBU(117mg, 0.75mmol) was added. The

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reaction solution was stirred at room temperature for 2 hours. The above solution was concentrated under the reduced pressure to remove tetrahydrofuran and concentrated was purified by column chromatography(Hexane : ether = 5:1) to obtain the titled compound.

5 yield : 76%

m.p. : 171-172°C

¹H NMR (CDCl₃): δ 3.41(4H,t), 3.81(6H,s), 4.17(3H,s), 4.21(4H,t),
6.12(1H,s), 6.20(1H,d), 7.38(1H,t), 7.54(1H,t), 7.74(1H,d), 7.81(1H,d),
8.96(1H,s)

10

Example 110

1-[(2-Methoxyquinolin-3-yl)aminothiocarbonyl]-4-(3,5-dimethylphenyl)
piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)thiocarbamate and

15 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with
the example 109 to obtain the titled compound.

yield : 79%

m.p. : 170-171°C

¹H NMR (CDCl₃): δ 2.30(6H,s), 3.38(4H,t), 4.09(3H,s), 4.17(4H,t),
20 6.63(3H,m), 7.38(1H,t), 7.54(1H,t), 7.72(1H,d), 7.81(1H,d), 8.96(1H,s)

Example 111

1-[(2-Methoxyquinolin-3-yl)aminothiocarbonyl]-4-(3,5-difluorophenyl)
piperazine:

25 Phenyl N-(2-methoxyquinolin-3-yl)thiocarbamate and

1-(3,5-difluorophenyl)piperazine were reacted by the same way with the
example 109 to obtain the titled compound.

yield : 78%

m.p. : 140-142°C

¹H NMR (CDCl₃): δ 3.44(4H,t), 4.20(4H,t), 4.25(3H,s), 6.33(2H,m),
30 6.45(1H,d), 7.41(1H,t), 7.56(1H,m), 7.72(1H,m), 7.97(1H,m), 8.96(1H,s)

Example 112

1-[(2-Methoxyquinolin-3-yl)aminothiocarbonyl]-4-(3,5-dichlorophenyl)

35 piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)thiocarbamate and

- 60 -

1-(3,5-dichlorophenyl)piperazine were reacted by the same way with the example 109 to obtain the titled compound.

yield : 62%

m.p.: 181-183°C

- 5 ¹H NMR (CDCl₃): δ 3.44(4H,t), 4.20(4H,t), 4.26(3H,s), 6.77(1H,s), 6.88(2H,t), 7.41(1H,t), 7.59(1H,t), 7.70(2H,m), 8.01(1H,t), 8.11(1H,s), 8.93(1H,s)

Example 113

- 10 1-[(2-Methoxyquinolin-3-yl)aminothiocarbonyl]-4-(3-methoxyphenyl) piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)thiocarbamate and 1-(3-methoxyphenyl)piperazine were reacted by the same way with the example 109 to obtain the titled compound.

- 15 yield : 81%

m.p. : oil phase

¹H NMR (CDCl₃): δ 3.17(4H,t), 3.89(3H,s), 4.17(4H,t), 6.90(4H,m), 7.34(1H,t), 7.48(1H,t), 7.70(1H,d), 7.77(1H,d), 8.80(1H,s)

- 20 Example 114 .

1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl) piperazine:

a) Phenyl N-(2-methylquinolin-3-yl)carbamate:

- 25 3-amino-2-methylquinoline(4g, 25mmol) and phenyl chloroformate(4.04g, 25mmol) were dissolved in methylene chloride and then was stirred at room temperature for 2 hrs. The mixture solution was concentrated under the reduced pressure to remove methylene chloride and purified by column chromatography(ethylacetate : hexane = 1:10) to obtain the
30 titled compound.

yield : 88%

¹H NMR (CDCl₃): δ 2.77(3H,s), 7.30-7.53(9H,m), 8.67(1H,s)

- b) 1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl) piperazine:

35 Phenyl N-(2-methylquinolin-3-yl)carbamate(140mg, 0.5mmol) and

1-(3,5-dimethoxyphenyl)piperazine(112mg, 0.5mmol) were dissolved in tetrahydrofuran and DBU(117mg, 0.75mmol) was added and then the mixture was stirred at room temperature for 2 hrs. The above solution was concentrated under the reduced pressure to remove tetrahydrofuran and purified by column chromatography(ethylacetate : hexane = 1:2) to obtain the titled compound.

yield : 84%

m.p. : 199-200°C

¹H NMR (CDCl₃): δ 2.81(3H,s), 3.30(4H,t), 3.76(4H,t), 3.80(6H,s), 6.08(1H,s), 6.12(2H,d), 7.48(1H,t), 7.62(1H,t), 7.71(1H,d), 8.03(1H,d), 8.59(1H,s)

Example 115

1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl) piperazine:

Phenyl N-(2-methylquinolin-3-yl)carbamate and

1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 114 to obtain the titled compound.

yield : 86%

m.p. : 230-232°C

¹H NMR (CDCl₃): δ 2.31(6H,s), 2.82(3H,s), 3.29(4H,t), 3.76(4H,t), 6.60(3H,s), 7.49(1H,t), 7.63(1H,t), 7.73(1H,d), 8.05(1H,d), 8.61(1H,s)

Example 116

1-[(2-methylquinolin-3-yl)aminocarbonyl]-4-(2,3-dimethylphenyl) piperazine:

Phenyl N-(2-methylquinolin-3-yl)carbamate and

1-(2,3-dimethylphenyl)piperazine were reacted by the same way with the example 114 to obtain the titled compound.

yield : 81%

m.p. : 169-170°C

¹H NMR (CDCl₃): δ 2.28(6H,d), 2.84(3H,s), 3.00(4H,t), 3.76(4H,t), 6.94(2H,m), 7.11(1H,t), 7.49(1H,t), 7.63(1H,t), 7.72(1H,d), 8.07(1H,d), 8.64(1H,s)

Example 117

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-difluorophenyl)
piperazine:

Phenyl N-(2-methylquinolin-3-yl)carbamate and

- 5 1-(3,5-difluorophenyl)piperazine were reacted by the same way with the
example 114 to obtain the titled compound.

yield : 81%

m.p. : 238-240°C

- ¹H NMR (CDCl₃): δ 2.81(3H,t), 3.34(4H,t), 3.77(4H,t), 6.32(1H,t),
10 6.39(2H,d), 7.49(1H,t), 7.63(1H,t), 7.72(1H,d), 8.03(1H,d), 8.58(1H,s)

Example 118

1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(3,5-dichlorophenyl)
piperazine:

- 15 Phenyl N-(2-methylquinolin-3-yl)carbamate and
1-(3,5-dichlorophenyl)piperazine were reacted by the same way with the
example 114 to obtain the titled compound.

yield : 65%

m.p. : 247-249°C

- ¹H NMR (CDCl₃): δ 2.79(3H,s), 3.33(4H,t), 3.75(4H,t), 6.78(2H,s),
20 6.87(1H,s), 7.49(1H,t), 7.63(1H,t), 7.72(1H,d), 8.56(1H,s)

Example 119

1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)

- 25 piperazine:

Phenyl N-(2-methylquinolin-3-yl)carbamate and

1-(2-methoxyphenyl)piperazine were reacted by the same way with the
example 114 to obtain the titled compound.

yield : 83%

- 30 m.p. : 135-136°C

¹H NMR (CDCl₃): δ 2.82(3H,s), 3.18(4H,t), 3.79(4H,t), 3.91(3H,s),
6.88(1H,d), 6.97(2H,s), 7.07(1H,m), 7.48(1H,t), 7.62(1H,t), 7.72(1H,d),
8.04(1H,d), 8.63(1H,s)

- 35 Example 120

1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(2-fluorophenyl)piperazine:

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Phenyl N-(2-methylquinolin-3-yl)carbamate and 1-(2-fluorophenyl)piperazine were reacted by the same way with the example 114 to obtain the titled compound.

yield : 84%

5 m.p. : 201-203°C

¹H NMR (CDCl₃): δ 2.84(3H,s), 3.20(4H,t), 3.80(4H,t), 6.99(2H,m), 7.07(2H,m), 7.49(1H,t), 7.62(1H,t), 7.71(1H,d), 8.04(1H,d), 8.62(1H,s)

Example 121

10 1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(2-chlorophenyl)piperazine:
Phenyl N-(2-methylquinolin-3-yl)carbamate and 1-(2-chlorophenyl)piperazine were reacted by the same way with the example 114 to obtain the titled compound.

yield : 72%

15 m.p. : 180-181°C

¹H NMR (CDCl₃): δ 2.83(3H,s), 3.16(4H,t), 3.80(4H,t), 7.04(3H,m), 7.40(1H,d), 7.49(1H,t), 7.63(1H,t), 7.71(1H,d), 8.05(1H,d), 8.62(1H,s)

Example 122

20 1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(2-methylthiophenyl)piperazine:

Phenyl N-(2-methylquinolin-3-yl)carbamate and 1-(2-methylthiophenyl)piperazine were reacted by the same way with the example 114 to obtain the titled compound.

25 yield : 76%

m.p. : 165-166°C

¹H NMR (CDCl₃): δ 2.45(3H,s), 2.85(3H,s), 3.11(4H,t), 3.79(4H,t), 7.05(1H,m), 7.15(3H,d), 7.49(1H,t), 7.63(1H,t), 7.69(1H,d), 8.07(1H,d), 8.62(1H,s)

30

Example 123

1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(2-methoxy-5-methylphenyl)piperazine:

Phenyl N-(2-methylquinolin-3-yl)carbamate and

35 1-(2-methoxy-5-methylphenyl)piperazine were reacted by the same way with the example 114 to obtain the titled compound.

yield : 80%

m.p. : oil phase

¹H NMR (CDCl₃): δ 2.30(3H,s), 2.72(3H,s), 3.17(4H,t), 3.70(4H,t),
3.87(3H,s), 6.77(1H,s), 6.82(2H,s), 7.73(4H,m), 8.60(1H,s)

5

Example 124

1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(1-naphthyl)piperazine:
Phenyl N-(2-methylquinolin-3-yl)carbamate and

1-(1-naphthyl)piperazine were reacted by the same way with the
10 example 114 to obtain the titled compound.

yield : 64%

m.p. : 220-222°C

¹H NMR (CDCl₃): δ 2.83(3H,s), 3.23(4H,t), 3.80(4H,t), 6.91(1H,s),
7.12(1H,d), 7.44(1H,d), 7.50(3H,m), 7.61(2H,m), 7.73(1H,d), 7.86(1H,d),
15 8.05(1H,d), 8.23(1H,d), 8.64(1H,s)

Example 125

1-[(2-Methylquinolin-3-yl)aminothiocabonyl]-4-(3,5-dimethoxyphenyl)
piperazine:

20

a) Phenyl N-(2-methylquinolin-3-yl)thiocarbamate:

3-Amino-2-methylquinoline(4g, 25mmol) and phenyl
chlorothionoformate(4.32g, 25mmol) were dissolved in methylene chloride
and then was stirred at room temperature for 2hours. The mixture
25 solution was concentrated under reduced pressure to remove methylene
chloride and purified by column chromatography(ethylacetate : hexane =
1 : 2) to obtain the titled compound.

yield : 78%

¹H NMR (CDCl₃): δ 2.77(3H,s), 7.09-7.90(9H,m), 9.14(1H,s)

30

b)

1-[(2-Methylquinolin-3-yl)aminothiocabonyl]-4-(3,5-dimethoxyphenyl)
piperazine:

Phenyl N-(2-methylquinolin-3-yl)thiocarbamate(147mg, 0.5mmol) and
35 1-(3,5-dimethoxyphenyl)piperazine(112mg, 0.5mmol) were dissolved in
anhydrous tetrahydrofuran and DBU(117mg, 0.75mmol) was added and

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then the mixture was stirred at room temperature for 2 hrs. The above solution was concentrated under the reduced pressure to remove tetrahydrofuran and purified by column chromatography(ethylacetate : hexane = 1 : 2) to obtain the titled compound.

5 yield : 86%

 m.p. : 211-212°C

¹H NMR (CDCl₃): δ 2.81(3H,s), 3.35(4H,t), 3.79(6H,s), 4.14(4H,t),
 6.07(3H,s), 7.49(2H,t), 7.68(2H,m), 8.01(1H,s), 8.07(1H,d)

10 Example 126

 1-[(2-Methylquinolin-3-yl)aminothiocarbonyl]-4-(3,5-dimethylphenyl)
 piperazine:

 Phenyl N-(2-methylquinolin-3-yl)thiocarbamate and

 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with

15 the example 125 to obtain the titled compound.

 yield : 81%

 m.p. : 196-197°C

¹H NMR (CDCl₃): δ 2.27(6H,s), 2.81(3H,s), 3.31(4H,t), 4.11(4H,t),
 6.53(2H,s), 6.58(1H,s), 7.48(2H,t), 7.67(2H,m), 7.96(1H,s), 8.04(1H,d)

20

 Example 127

 1-[(2-Methylquinolin-3-yl)aminothiocarbonyl]-4-(3,5-difluorophenyl)
 piperazine:

 Phenyl N-(2-methylquinolin-3-yl)thiocarbamate and

25 1-(3,5-difluorophenyl)piperazine were reacted by the same way with the
 example 125 to obtain the titled compound.

 yield : 74%

 m.p. : 211-213°C

¹H NMR (CDCl₃): δ 2.85(3H,s), 3.43(4H,t), 4.22(4H,t), 6.33(2H,m),
30 7.49(1H,t), 7.64(1H,d), 7.72(1H,t), 8.16(2H,m)

 Example 128

 1-[[2-(Pyridin-2-yl)quinolin-4-yl]aminocarbonyl]-4-(3,5-
 dimethoxyphenyl)piperazine:

35 Phenyl N-[2-(pyridin-3-yl)quinolin-4-yl]carbamate(171mg, 0.5mmol) and
 1-(3,5-dimethoxyphenyl)piperazine(111mg, 0.5mmol) were dissolved in

- 66 -

anhydrous tetrahydrofuran and DBU(117mg, 0.75mmol) was added and then the mixture was stirred at room temperature for 2hrs. The above solution was concentrated under the reduced pressure to remove tetrahydrofuran and purified by column chromatography

5 (dichloromethane : methanol=20:1) to obtain the titled compound.
yield : 73%

m.p. : 97-98°C

¹H NMR (CDCl₃): δ 3.34(4H,t), 3.79(6H,s), 3.90(4H,t), 6.07(1H,s),
6.12(2H,s), 7.43(1H,t), 7.50(1H,t), 7.68(1H,t), 7.93(1H,t), 8.26(1H,d),
10 8.59(1H,d), 8.80(1H,d), 8.98(1H,s)

Mass(EI) m/z : Calcd for C₃₁H₂₇N₅O₃ 517.2113, found 517.3244

Example 129

1-([2-(Pyridin-3-yl)quinolin-4-yl]aminocarbonyl)-4-(3,5-
15 dimethoxyphenyl)piperazine:

Phenyl N-[2-pyridin-3-yl]quinolin-4-yl]carbamate(171mg, 0.5mmol) and
1-(3,5-dimethoxyphenyl)piperazine(111mg, 0.5mmol) were dissolved in
anhydrous tetrahydrofuran and DBU(117mg, 0.75mmol) was added and
then the mixture was stirred at room temperature for 2 hours. The
20 above solution was concentrated under the reduced pressure to remove
tetrahydrofuran and purified by column chromatography
(dichloromethane : methanol = 20:1) to obtain the titled compound.
yield : 67%

m.p. : 95-96°C

25 ¹H NMR (CDCl₃): δ 3.36(4H,t), 3.87(6H,s), 3.90(4H,t), 6.08(1H,s),
6.12(2H,s), 7.50(1H,t), 7.71(1H,t), 7.93(1H,t), 8.25(1H,d), 8.53(1H,d),
8.67(1H,s), 8.73(1H,d), 9.35(1H,s)

Example 130

30 1-([2-Thien-2-yl]quinolin-4-yl]aminocarbonyl)-4-(3,5-dimethoxyphenyl)
piperazine:

Phenyl N-[2-(thien-2-yl)quinolin-4-yl]carbamate(173mg, 0.5mmol) and
1-(3,5-dimethoxyphenyl)piperazine(111mg, 0.5mmol) were dissolved in
anhydrous tetrahydrofuran and DBU(117mg, 0.75mmol) was added. The
35 resulting mixture was stirred at room temperature for 2 hours,
concentrated under the reduced pressure to remove tetrahydrofuran and

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purified by column chromatography(ethylacetate : hexane = 1:1) to obtain the titled compound.

yield : 61%

m.p. : oil phase

- 5 ¹H NMR (CDCl₃): δ 3.37(4H,t), 3.59(6H,s), 3.97(4H,t), 7.01(3H,m), 7.49(1H,t), 7.69(1H,t), 7.93(1H,t), 8.20(1H,d), 8.52(1H,d), 8.64(1H,s), 8.71(1H,d), 9.35(1H,s)

Example 131

- 10 1-([2-(Pyridin-3-yl)quinolin-4-yl]aminocarbonyl)-4-(3,5-dimethylphenyl) piperazine:

Phenyl N-[2-(pyridin-3-yl)quinolin-4-yl]carbamate(171mg, 0.5mmol) and 1-(3,5-dimethylphenyl)piperazine(95mg, 0.5mmol) were dissolved in anhydrous tetrahydrofuran and DBU(117mg, 0.75mmol) was added. The
15 resulting mixture was stirred at room temperature for 2 hours, concentrated under the reduced pressure to remove tetrahydrofuran, and purified by column chromatography(ethylacetate : hexane =1:1) to obtain the titled compound.

yield : 64%

- 20 m.p. : 211-213°C

¹H NMR (CDCl₃): δ 2.31(6H,s), 3.32(4H,t), 3.85(4H,t), 6.61(3H,s), 7.47(1H,t), 7.55(1H,t), 7.72(1H,t), 7.86(1H,t), 8.25(1H,d), 8.53(1H,d), 8.66(1H,s), 8.72(1H,d), 9.37(1H,s)

25 Example 132

1-[N-(5,6-Dimethyl-2-methoxypyridin-3-yl)-N-methylaminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine(100mg, 0.25mmol) was dissolved in
30 dimethylformamide(15ml) and thereto sodium hydride(6.0mg, 0.25mmol) was added. The resulting mixture was stirred at room temperature for 15 min and thereto iodomethane(35mg, 0.25mmol) was added. The resulting mixture was stirred at room temperature for 16 hrs, concentrated under the reduced pressure to remove dimethylformamide,
35 and purified by column chromatography(ethylacetate : hexane=1:2) to obtain the titled compound.

yield : 94%

m.p. : oil phase

^1H NMR(CDCl_3) δ : 2.17(3H,s), 2.38(3H,s), 2.92(4H,t), 3.04(3H,s),
3.29(4H,t), 3.74(6H,s), 3.96(3H,s), 6.00(3H,m), 7.08(1H,s)

5

Example 133

1-[N-Ethyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

10 1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine(100mg, 0.25mmol) was dissolved in dimethylformamide(15ml) and thereto sodium hydride(6.0mg, 0.25mmol) was added, followed by stirring at room temperature for 15 min and then iodoethane(39.2mg, 0.25mmol) was added. The resulting mixture was stirred at room temperature for 16 hrs, concentrated under the
15 reduced pressure to remove dimethylformamide, and purified by column chromatography(ethylacetate : hexane=1:2) to obtain the titled compound.
yield : 86%

m.p. : oil phase

20 ^1H NMR(CDCl_3) δ : 1.08(3H,t), 2.04(3H,s), 2.38(3H,s), 2.90(4H,t),
3.26(4H,t), 3.52(2H,q), 3.74(6H,s), 5.99(3H,m), 7.06(1H,s)

Example 134

1-[N-Isopropyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

25 1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine(100mg, 0.25mmol) was dissolved in dimethylformamide(15ml) and thereto sodium hydride(6.0mg, 0.25mmol) was added, followed by stirring at room temperature for 15 min, and then 2-iodopropane(42mg, 0.25mmol) was added. The resulting mixture
30 was stirred at room temperature for 16 hrs, concentrated under the reduced pressure to remove dimethylformamide, purified by column chromatography(ethylacetate : hexane=1:2) to obtain the titled compound.
yield : 78%

m.p. : oil phase

35 ^1H NMR(CDCl_3) δ : 1.13(6H,d), 2.19(3H,s), 2.38(3H,s), 2.82(4H,t),
3.26(4H,t), 3.74(6H,s), 3.89(3H,s), 4.27(1H,m), 6.06(1H,s), 6.10(2H,d),

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7.07(1H,s), 8.14(1H,s)

Mass(EI) m/z : Calcd for C₂₄H₃₄N₄O₄ 442.2580, found 442.2538

Example 135

- 5 1-[N-(5,6-Dimethyl-2-methoxypyridin-3-yl)-N-methylaminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

- 10 yield : 97%

m.p. : oil phase

¹H NMR(CDCl₃) δ : 2.15(6H,s), 2.23(3H,s), 2.37(3H,s), 2.89(4H,t), 3.04(3H,s), 3.30(4H,t), 3.97(3H,s), 6.46(3H,m), 7.08(1H,s)

- 15 Example 136

1-[N-(5,6-Dimethyl-2-methoxypyridin-3-yl)-N-methylaminocarbonyl]-4-(2-methoxyphenyl)piperazine:

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

- 20

yield : 94%

m.p. : 131-132°C

¹H NMR(CDCl₃) δ : 2.16(3H,s), 2.38(3H,s), 2.80(4H,t), 3.05(3H,s), 3.35(4H,t), 3.82(3H,s), 3.97(3H,s), 6.83(4H,m), 7.08(1H,s)

- 25

Example 137

1-[N-Ethyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine:

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine was reacted by the same way with the example 133 to obtain the titled compound.

- 30

yield : 87%

m.p. : 112-113°C

¹H NMR(CDCl₃) δ : 1.08(3H,t), 2.16(3H,s), 2.38(3H,s), 2.77(4H,t),

- 35 3.31(4H,t), 3.58(2H,q), 3.81(3H,s), 3.96(3H,s), 6.88(4H,m), 7.06(1H,s)

Example 138

1-[N-Benzyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine:

- 1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine(100mg, 0.27mmol) was dissolved in dimethylformamide(15ml) and thereto sodium hydride(6.5mg, 0.27mmol) was added, followed by stirring at room temperature for 1hr, and successively benzyl bromide(46.2mg, 0.27mmol) was added. The resulting mixture was stirred at room temperature for 16 hrs, concentrated under the reduced pressure and purified by column chromatography(ethylacetate : hexane = 1: 2) to obtain the titled compound.

yield : 93%

m.p. : oil phase

- ¹H NMR(CDCl₃) δ : 2.08(3H,s), 2.35(3H,s), 2.85(4H,t), 3.32(4H,t), 3.81(3H,s), 3.96(3H,s), 4.76(2H,s), 6.96(4H,m), 7.41(5H,m)

Example 139

- 1-[N-Cyclopropylmethyl]-N-(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine:
1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine(100mg, 0.26mmol) was dissolved in dimethylformamide(15ml) and thereto sodium hydride(6.2mg, 0.26mmol) was added, followed by stirring at room temperature for 15 min, and successively bromomethylcyclopropane(21.8mg, 0.26mmol) was added. The resulting mixture was stirred at room temperature for 16 hrs, concentrated under the reduced pressure and purified by column chromatography(ethylacetate : hexane = 1: 2) to obtain the titled compound.

- yield : 78%

m.p. : oil phase

¹H NMR(CDCl₃) δ : 0.34(2H,m), 0.49(2H,m), 1.35(1H,m), 2.85(4H,t), 3.28(4H,t), 3.40(2H,s), 3.89(3H,s), 3.97(3H,s), 6.97(4H,m), 7.11(1H,s)

Example 140

1-[N-(5,6-Dimethyl-2-methoxypyridin-3-yl)-N-methylaminocarbonyl]-4-

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(5-methoxy-2-methylphenyl)piperazine:

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(5-methoxy-2-methylphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

5 yield : 74%

 m.p. : 91-93°C

¹H NMR(CDCl₃) δ : 2.15(3H,s), 2.18(3H,s), 2.39(3H,s), 2.67(4H,t),
 3.05(3H,s), 3.30(4H,t), 3.75(3H,s), 3.97(3H,s), 6.48(3H,m), 7.10(1H,s)

10 Example 141

 1-[N-Ethyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(5-methoxy-2-methylphenyl)piperazine:

 1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(5-methoxy-2-methylphenyl)piperazine was reacted by the same way with the

15 example 133 to obtain the titled compound.

 yield : 94%

 m.p. : oil phase

¹H NMR(CDCl₃) δ : 1.09(3H,t), 2.15(3H,s), 2.18(3H,s), 2.39(3H,s),
 2.60(4H,t), 3.27(4H,t), 3.59(2H,q), 3.75(3H,s), 3.96(3H,s), 6.45(3H,m),

20 7.08(1H,s)

 Example 142

 1-[N-Benzyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(5-methoxy-2-methylphenyl)piperazine:

25 1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(5-methoxy-2-methylphenyl)piperazine was reacted by the same way with the example 138 to obtain the titled compound.

 yield : 97%

 m.p. : oil phase

30 ¹H NMR(CDCl₃) δ : 1.25(3H,t), 2.08(3H,s), 2.14(3H,s), 2.35(3H,s),
 2.60(4H,t), 3.32(4H,t), 3.74(3H,s), 3.95(3H,s), 4.66(2H,s), 6.44(4H,m),
 6.96(5H,m), 7.12(1H,s)

 Example 143

35 1-[N-(5-Ethyl-2-methoxy-6-methylpyridin-3-yl)-N-methylamino
 carbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

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1-[(5-Ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

yield : 87%

5 m.p. : 78-79°C

¹H NMR(CDCl₃) δ : 1.14(3H,t), 2.41(3H,s), 2.52(2H,q), 2.91(4H,t), 3.02(3H,s), 3.28(4H,t), 3.74(6H,s), 3.98(3H,s), 5.98(3H,m), 7.11(1H,s)

Mass(EI) m/z : Calcd for C₂₃H₃₂N₄O₄ 428.2423, found 428.2434

10 Example 144

1-[N-(5-Ethyl-2-methoxy-6-methylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[(5-Ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the

15 example 132 to obtain the titled compound.

yield : 84%

m.p. : 86-87°C

¹H NMR(CDCl₃) δ : 1.14(3H,t), 2.23(6H,s), 2.45(3H,s), 2.58(2H,q), 2.87(4H,t), 3.05(3H,s), 3.30(4H,t), 3.98(3H,s), 6.46(3H,m), 7.11(1H,s)

20 Mass(EI) m/z : Calcd for C₂₃H₃₂N₄O₂ 396.2525, found 396.2575

Example 145

1-[N-Ethyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

25 1-[(5-Ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 133 to obtain the titled compound.

yield : 86%

m.p. : 84-85°C

30 ¹H NMR(CDCl₃) δ : 1.13(6H,m), 2.23(6H,s), 2.41(3H,s), 2.58(2H,q), 2.85(4H,t), 3.26(4H,t), 3.46(2H,q), 3.96(3H,s), 6.45(3H,m), 7.08(1H,s)

Example 146

1-[N-(2-Methoxy-6-methyl-5-propylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

35 1-[(2-Methoxy-6-methyl-5-propylpyridin-3-yl)aminocarbonyl]-4-

- 73 -

(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

yield : 89%

m.p. : oil phase

- 5 ^1H NMR(CDCl_3) δ : 1.01(3H,t), 1.78(2H,m), 2.21(3H,s), 2.78(2H,t), 3.78(6H,s), 3.86(4H,t), 3.99(3H,s), 4.00(3H,s), 4.22(4H,t), 6.01(3H,m), 7.02(1H,s)

Example 147

- 10 1-[N-(6-Ethyl-2-methoxy-5-methylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
1-[(6-Ethyl-2-methoxy-5-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

- 15 yield : 85%

m.p. : oil phase

^1H NMR(CDCl_3) δ : 2.21(3H,t), 2.21(3H,s), 2.45(2H,q), 3.21(4H,t), 3.40(3H,s), 3.67(4H,t), 3.77(6H,s), 4.01(3H,s), 6.07(3H,m), 6.96(1H,s), 8.07(1H,s)

20

Example 148

- 1-[N-(2-Methoxy-5-methyl-6-propylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
1-[(2-Methoxy-5-methyl-6-propylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

yield : 86%

m.p. : 106-107°C

- 30 ^1H NMR(CDCl_3) δ : 0.98(3H,t), 1.73(2H,q), 2.18(3H,s), 2.63(2H,t), 2.92(4H,t), 3.05(3H,s), 3.29(4H,t), 3.74(6H,s), 3.96(3H,s), 6.00(3H,m), 7.11(1H,s)

Mass(EI) m/z : Calcd for $\text{C}_{24}\text{H}_{34}\text{N}_4\text{O}_4$ 442.2580, found 442.2543

Example 149

- 35 1-[N-(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

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1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

yield : 89%

5 m.p. : oil phase

¹H NMR(CDCl₃) δ : 2.50(3H,s), 2.70(3H,s), 2.97(4H,t), 3.09(3H,s), 3.33(4H,t), 3.75(6H,s), 4.06(3H,s), 6.03(3H,m), 7.72(1H,s)

Mass(EI) m/z : Calcd for C₂₃H₃₀N₄O₅ 442.2216, 442.2229

10 Example 150

1-[N-Ethyl-N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the

15 example 133 to obtain the titled compound.

yield : 87%

m.p. : oil phase

¹H NMR(CDCl₃) δ : 1.09(3H,t), 2.49(3H,s), 2.70(3H,s), 3.00(4H,t), 3.32(4H,t), 3.77(6H,s), 4.01(3H,s), 4.09(2H,q), 5.98(3H,m), 7.76(1H,s)

20

Example 151

1-[N-(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-

25 (3,5-dimethylphenyl)piperazine was reacted by the same with the example 132 to obtain the titled compound.

yield : 88%

m.p. : oil phase

¹H NMR(CDCl₃) δ : 2.24(6H,s), 2.50(3H,s), 2.70(3H,s), 2.93(4H,t),

30 3.09(3H,s), 3.28(4H,t), 4.06(3H,s), 6.46(3H,m), 7.73(1H,s)

Example 152

1-[N-[5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]-N-methyl aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

35 1-[N-(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethoxyphenyl)piperazine(0.47mmol) was dissolved in

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anhydrous ethanol(15ml) and thereto sodium borohydride(17.3mg) was added, then followed by stirring at room temperature for 2 hrs. The resulting mixture was concentrated under the reduced pressure to remove ethanol and purified by column chromatography(ethylacetate :
5 hexane = 2:1) to obtain the titled compound.
yield : 97%

m.p. : oil phase

¹H NMR(CDCl₃) δ : 1.14(3H,d), 2.44(3H,s), 2.93(4H,t), 3.06(3H,s),
3.30(4H,t), 3.74(6H,s), 3.98(3H,s), 5.03(1H,q), 6.02(3H,m), 7.50(1H,s)

10

Example 153

1-{N-Ethyl-N-[5-(1-hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl}-4-(3,5-dimethoxyphenyl)piperazine;

15 1-[N-Ethyl-N-(5-cetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 152 to obtain the titled compound.

yield : 96%

m.p. : oil phase

20 ¹H NMR(CDCl₃) δ : 1.09(3H,t), 1.41(3H,d), 2.44(3H,s), 2.91(4H,t),
3.27(4H,t), 3.54(1H,q), 3.74(6H,s), 3.96(3H,s), 5.03(1H,q), 6.02(3H,m),
8.46(1H,s)

Example 154

25 1-{N-[5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]-N-methylaminocarbonyl}-4-(3,5-dimethylphenyl)piperazine:

1-[N-Methyl-N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 152 to obtain the titled compound.

yield : 97%

30 m.p. : oil phase

¹H NMR(CDCl₃) δ : 1.41(3H,d), 2.24(6H,s), 2.44(3H,s), 2.91(4H,t),
3.06(3H,s), 3.26(4H,t), 3.99(3H,s), 5.03(1H,q), 6.49(3H,m), 7.50(1H,s)

Example 155

35 1-{N-[5-(1-Hydroxy-1-methylethyl)-2-methoxy-6-methylpyridin-3-yl]-N-methylaminocarbonyl}-4-(3,5-dimethoxyphenyl)piperazine:

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1-[N-Methyl-N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)amino carbonyl]-4-(3,5-dimethoxyphenyl)piperazine(221mg, 0.5mmol) was dissolved in tetrahydrofuran(10ml) and thereto methyl magnesium bromide(0.50ml, 1.50mmol). The resulting mixture was refluxed for 15
5 hrs, concentrated under the reduced pressure to remove used solvent, extracted with ethylacetate, filtered to dryness, and purified by column chromatography(ethylacetate : hexane =1:2) to obtain the titled compound.
yield : 92%

10 m.p. : oil phase

¹H NMR(CDCl₃) δ: 1.59(6H,s), 2.66(3H,s), 2.93(4H,t), 3.06(3H,s), 3.30(4H,t), 3.74(6H,s), 3.99(3H,s), 6.03(3H,m), 7.45(1H,s)

Example 156

15 1-(N-[5-(1-Hydroxy-1-methylpropyl)-2-methoxy-6-methylpyridin-3-yl]-N-methylaminocarbonyl)-4-(3,5-dimethylphenyl)piperazine:
1-[N-Methyl-N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)amino carbonyl]-4-(3,5-dimethylphenyl)piperazine(213mg, 0.5mmol) was dissolved in tetrahydrofuran(10ml) and thereto methyl magnesium
20 bromide(0.50ml, 1.50mmol) was added slowly, then refluxed for 15 hrs. The resulting mixture was concentrated under the reduced pressure to remove the used solvent, extracted with ethylacetate, filtered to dryness, and purified by column chromatography(ethylacetate : hexane =1:2) to obtain the titled compound.

25 yield : 88%

m.p. : oil phase

¹H NMR(CDCl₃) δ: 0.79(3H,t), 1.58(3H,s), 1.85(2H,q), 2.61(3H,s), 2.99(4H,t), 3.07(3H,s), 3.30(4H,t), 3.76(6H,s), 6.12(3H,m), 7.47(1H,s)

30 Example 157

1-(N-[2-Methoxy-5-(1-methoxyethyl)-6-methylpyridin-3-yl]-N-methyl aminocarbonyl)-4-(3,5-dimethoxyphenyl)piperazine:

1-(N-[5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]amino carbonyl)-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same
35 way with the example 132 to obtain the titled compound.

yield : 95%

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m.p. : 117-119°C

¹H NMR(CDCl₃) δ : 1.34(3H,t), 2.43(3H,s), 2.94(4H,t), 3.06(3H,s),
3.18(3H,s), 3.30(4H,t), 3.74(6H,s), 3.99(3H,s), 4.44(1H,q), 6.02(3H,m),
7.37(1H,s)

5

Example 158

1-[N-(2-Methoxy-6-methyl-5-vinylpyridin-3-yl)-N-methylamino
carbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

10 1-[(2-Methoxy-6-methyl-5-vinylpyridin-3-yl)aminocarbonyl]-4-
(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the
example 132 to obtain the titled compound.

yield : 94%

m.p. : oil phase

15 ¹H NMR(CDCl₃) δ : 2.46(3H,s), 2.93(4H,t), 3.07(3H,s), 3.30(4H,t),
3.73(6H,s), 3.99(3H,s), 5.25(1H,d), 5.48(1H,d), 6.01(3H,m), 6.78(1H,s),
7.43(1H,s)

Example 159

20 1-[N-(2-Methoxy-6-methyl-5-vinylpyridin-3-yl)-N-methylamino
carbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[(2-Methoxy-6-methyl-5-vinylpyridin-3-yl)aminocarbonyl]-4-
(3,5-dimethylphenyl)piperazine was reacted by the same way with the
example 132 to obtain the titled compound.

yield : 89%

25 m.p. : oil phase

¹H NMR(CDCl₃) δ : 2.24(6H,s), 2.43(3H,s), 2.90(4H,t), 3.04(3H,s),
3.27(4H,t), 3.99(3H,s), 5.23(1H,d), 5.45(1H,d), 6.05(3H,m), 6.77(1H,s),
7.40(1H,s)

30 Example 160

1-[N-Ethyl-N-(2-methoxy-6-methyl-5-vinylpyridin-3-yl)aminocarbonyl]
-4-(3,5-dimethoxyphenyl)piperazine:

1-[(2-Methoxy-6-methyl-5-vinylpyridin-3-yl)aminocarbonyl]-4-
(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the
35 example 133 to obtain the titled compound.

yield : 92%

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m.p. : oil phase

¹H NMR(CDCl₃) δ : 1.09(3H,t), 2.43(3H,s), 2.94(4H,t), 3.28(4H,t),
3.77(6H,s), 4.01(3H,s), 4.11(2H,q), 5.25(1H,d), 5.49(1H,d), 5.98(3H,m),
6.77(1H,s), 7.44(1H,s)

5

Example 161

1-[N-(5-Isopropenyl-2-methoxy-6-methylpyridin-3-yl)-N-methylamino
carbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

10 1-[(5-Isopropenyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-
(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the
example 132 to obtain the titled compound.

yield : 92%

m.p. : oil phase

15 ¹H NMR(CDCl₃) δ : 1.98(3H,s), 2.43(3H,s), 2.92(4H,t), 3.06(3H,s),
3.29(4H,t), 3.74(6H,s), 3.99(3H,s), 4.84(1H,s), 5.30(1H,s), 6.01(3H,m),
7.10(1H,s)

Example 162

20 1-[N-(5-Isopropenyl-2-methoxy-6-methylpyridin-3-yl)-N-methylamino
carbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[(5-Isopropenyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-
(3,5-dimethylphenyl)piperazine was reacted by the same way with the
example 132 to obtain the titled compound.

yield : 91%

25 m.p. : oil phase

¹H NMR(CDCl₃) δ : 1.98(3H,s), 2.24(6H,s), 2.43(3H,s), 2.90(4H,t),
3.06(3H,s), 3.28(4H,t), 4.00(3H,s), 4.84(1H,s), 5.19(1H,s), 6.46(3H,m),
7.10(1H,s)

30 Example 163

Ethyl 2-([(4-(3,5-dimethoxyphenyl)piperazino]carbonyl)(5-acetyl-2-
methoxy-6-methylpyridin-3-yl)amino)acetate:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-
(3,5-dimethoxyphenyl)piperazine(200mg, 0.5mmol) was dissolved in
35 dimethylformamide(15ml) and thereto sodium hydride(18.5mg, 0.5mmol)
was added, then followed by stirring at room temperature for 15 min.

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and ethylbromoacetate(83.5mg, 0.5mmol) was added. The resulting mixture was stirred at room temperature for 3 hrs, concentrated under the reduced pressure to remove the used solvent, and purified by column chromatography(ethylacetate : hexane =1:2) to obtain the titled compound.

5 yield : 84%
 m.p. : oil phase
 ¹H NMR(CDCl₃) δ : 1.26(3H,t), 2.51(3H,s), 2.69(3H,s), 3.04(4H,t),
 3.43(4H,t), 3.75(6H,s), 4.05(3H,s), 4.15(2H,q), 4.19(2H,s), 6.08(3H,s),
10 7.96(1H,s)

Example 164
Ethyl 2-([4-(3,5-dimethylphenyl)piperazino]carbonyl)(5-acetyl-2-methoxy-6-methylpyridin-3-yl)amino)acetate:

15 1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 163 to obtain the titled compound.

 yield : 80%
 m.p. : oil phase

20 ¹H NMR(CDCl₃) δ : 1.25(3H,t), 2.56(3H,s), 2.69(3H,s), 3.00(4H,t),
 3.29(4H,t), 3.78(6H,s), 4.06(3H,s), 4.18(2H,s), 5.99(3H,m), 7.98(1H,s)

Example 165
2-([4-(3,5-Dimethoxyphenyl)piperazino]carbonyl)(5-acetyl-2-methoxy-6-methylpyridin-3-yl)amino)acetic acid:

25 Ethyl ([4-(3,5-dimethoxyphenyl)piperazino]carbonyl)(5-acetyl-2-methoxy-6-methylpyridin-3-yl)amino)acetate(200mg, 0.38mmol) was dissolved in mixed solvent of dioxane : distilled water =4:1(15ml), and lithium hydroxide hydrate(48.1mg, 1.14mmol) was added, then followed by

30 stirring at room temperature for 3 hrs. The resulting mixture was made acidic with 1N-HCl, extracted with ethylacetate, filtered to dryness, concentrated under the reduced pressure and purified by column chromatography(ethylacetate : hexane = 1 : 2) to obtain the titled compound.

35 yield : 94%
 m.p. : 135-137°C

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¹H NMR(CDCl₃) δ : 2.52(3H,s), 2.69(3H,s), 3.11(4H,t), 3.49(4H,t), 3.74(6H,s), 4.05(3H,s), 4.24(2H,s), 6.15(3H,m), 7.83(1H,s)

Example 166

5 Ethyl 2-(((4-(3,5-dimethoxyphenyl)piperazino]carbonyl)[5-(1-hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]amino)acetate:
Ethyl 2-(((4-(3,5-dimethoxyphenyl)piperazino]carbonyl)(5-acetyl-2-methoxy-6-methylpyridin-3-yl)amino)acetate was reacted by the same way with the example 152 to obtain the titled compound.

10 yield : 97%

m.p. : 125-127°C

¹H NMR(CDCl₃) δ : 1.26(3H,t), 1.42(3H,d), 2.44(3H,s), 3.04(4H,t), 3.31(4H,t), 3.75(6H,s), 3.97(3H,s), 4.16(2H,q), 4.19(2H,s), 6.15(3H,m), 7.69(1H,s)

15

Example 167

Ethyl 2-(((4-(3,5-dimethoxyphenyl)piperazino]carbonyl)[5-(1-hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]amino)acetate:
Ethyl 2-(((4-(3,5-dimethoxyphenyl)piperazino]carbonyl)[5-(1-hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]amino)acetate was reacted by the same way with the example 164 to obtain the titled compound.

yield : 92%

m.p. : oil phase

25 ¹H NMR(CDCl₃) δ : 1.41(3H,d), 2.44(3H,s), 2.98(4H,t), 3.36(4H,t), 3.74(6H,s), 3.98(3H,s), 4.40(2H,s), 5.00(1H,q), 6.08(3H,m), 7.69(1H,s)

Example 168

Ethyl 2-(((4-(3,5-dimethylphenyl)piperazino]carbonyl)[5-(1-hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]amino)acetate:
Ethyl 2-(((4-(3,5-dimethylphenyl)piperazino]carbonyl)(5-acetyl-2-methoxy-6-methylpyridin-3-yl)amino)acetate was reacted by the same way with the example 152 to obtain the titled compound.

yield : 94%

35 m.p. : 68-70°C

¹H NMR(CDCl₃) δ : 1.13(3H,t), 1.47(3H,d), 2.33(6H,s), 2.44(3H,s),

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2.95(4H,t), 3.30(4H,t), 3.98(3H,s), 4.10(2H,q), 5.01(1H,q), 6.46(3H,m),
7.71(1H,s)

Example 169

5 2-([4-(3,5-Dimethylphenyl)piperazino]carbonyl)[5-(1-hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]amino)acetic acid:
Ethyl 2-([4-(3,5-dimethylphenyl)piperazino]carbonyl)[5-(1-hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]amino)acetate was
reacted by the same way with the example 165 to obtain the titled
10 compound.

yield : 92%

m.p. : 114-116°C

¹H NMR(CDCl₃) δ : 1.40(3H,d), 2.23(6H,s), 2.40(3H,s), 2.91(4H,t),
3.21(4H,t), 3.98(3H,s), 4.06(2H,s), 4.90(1H,q), 6.50(3H,m), 6.51(1H,s)

15

Example 170

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-phenylpiperazine
a) 3,4-Dimethyl anisole:

To 3,4-dimethylphenol(19.3g, 0.16mol), methanol(150ml) and KOH(9.65g,
20 0.25mol) were added and then refluxed for 2hrs. Methyl iodide(36.5g,
0.25mol) was added thereto, refluxed for 3 hours and then followed by
addition of water(150ml). The resulting mixture was extracted with
ethylacetate and purified by column chromatography to obtain the
titled compound.

25 yield : 81%

¹H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.24(3H,s), 3.77(3H,s),
6.71(2H,m), 6.97(1H,s)

b) 4,5-Dimethyl-2-nitroanisole:

Trifluoroacetic acid(250ml) was added into 3,4-dimethylanisole(17.1g,
30 0.13mol), successively sodium nitrite(16.6g, 0.24mol) was added slowly
in water bath, and stirred at room temperature for 14 hrs. After
trifluoroacetic acid was removed and water was added thereto, the
resulting mixture was extracted with ether, and purified by column
chromatography to obtain the titled compound.

35 yield : 55%

¹H NMR(500MHz, CDCl₃): δ 2.25(3H,s), 2.32(3H,s), 3.94(3H,s),

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6.85(1H,s), 7.70(1H,s)

c) 4,5-Dimethyl-2-methoxyaniline:

Tetrahydrofuran(100ml) and ethanol(40ml) were added into
4,5-dimethyl-2-nitroanisole(7.80g, 0.043mol) and then added 10%

- 5 Pd/activated carbon(0.57g) slowly, hydrogenated for 5 hrs. The reaction
was completed by the same way with the above and the resulting
product was purified by column chromatography to obtain the titled
compound.

yield : 82%

- 10 ^1H NMR(500MHz, CDCl_3): δ 2.23(3H,s), 2.27(3H,s), 3.90(3H,s),
6.80(1H,s), 7.68(1H,s)

d) Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate:

- To 4,5-dimethyl-2-methoxyaniline(4.50g, 0.03mol), methylene
chloride(100ml) was added and phenyl chloroformate(4.80g, 0.03mol) was
15 added slowly. The resulting solution was stirred for 2 hrs and thereto
water(150ml) was added, and extracted with methylene chloride and
purified by column chromatography to obtain the titled compound.

yield : 98%

- ^1H NMR(500MHz, CDCl_3): δ 2.24(3H,s), 2.27(3H,s), 3.89(3H,s),
20 6.85(1H,s), 7.20(5H,m), 7.90(1H,s)

e) 1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-phenylpiperazine:

- Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate(5.422g, 0.02mol) and
1-phenylpiperazine(3.44g, 0.02mol) were dissolved in
tetrahydrofuran(10ml). After DBU(3.04g, 0.02mol) was added, the
25 resulting solution was stirred at room temperature for 2 hrs,
concentrated and purified by column chromatography to obtain the
titled compound.

yield : 85%

m.p.: 143-144°C

- 30 ^1H NMR(500MHz, CDCl_3): δ 2.20(3H,s), 2.21(3H,s), 3.25(4H,t), 3.67(4H,t),
3.85(3H,s), 6.64(1H,s), 6.94(3H,m), 6.99(1H,s), 7.29(1H,t), 7.91(1H,s)

Example 171

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-

- 35 (3,5-dimethoxyphenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and

- 83 -

1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.

yield : 85%

m.p. : 119-120°C

- 5 ¹H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.21(3H,s), 3.27(4H,t), 3.70(4H,t), 3.79(6H,s), 3.85(3H,s), 6.17(2H,m), 6.65(1H,s), 6.98(1H,s), 7.90(1H,s)
Mass(EI) m/z : Calcd for C₂₂H₂₃N₃O₄ 399.2158, found 399.2168

Example 172

- 10 1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and

1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.

- 15 yield : 88%

m.p. : 177-178°C

¹H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.21(3H,s), 2.29(6H,s), 3.23(4H,t), 3.66(4H,t), 3.85(3H,s), 6.58(2H,m), 6.65(1H,s), 6.99(1H,s), 7.92(1H,s)

- 20 Mass(EI) m/z : Calcd for C₂₂H₂₃N₃O₂ 367.2259, found 367.2290

Example 173

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(2,3-dimethylphenyl)piperazine:

- 25 Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and

1-(2,3-dimethylphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.

yield : 95%

m.p. : 140-142°C

- 30 ¹H NMR(500MHz, CDCl₃): δ 2.21(3H,s), 2.22(3H,s), 2.27(3H,s), 2.29(3H,s), 2.95(4H,t), 3.67(4H,t), 3.85(3H,s), 6.65(1H,s), 7.01(3H,m), 7.93(1H,s)

Example 174

- 35 1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(2,3,5,6-tetramethylphenyl)piperazine:

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Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(2,3,5,6-tetramethylphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.

yield : 93%

5 m.p. : oil phase

¹H NMR(500MHz, CDCl₃): δ 2.20(9H,s), 2.21(9H,s), 3.17(4H,t), 3.63(4H,t), 3.84(3H,s), 6.64(1H,s), 6.84(1H,s), 7.95(1H,s)

Example 175

10 1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-difluorophenyl) piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(3,5-difluorophenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.

15 yield : 89%

m.p. : 102-103°C

¹H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.22(3H,s), 3.29(4H,t), 3.68(4H,t), 3.85(3H,s), 6.65(1H,s), 6.97(3H,m), 7.89(1H,s)

20 Example 176

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(2-chlorophenyl) piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(2-chlorophenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.

25 yield : 90%

m.p. : 176-177°C

¹H NMR(500MHz, CDCl₃): δ 2.21(3H,s), 2.22(3H,s), 3.10(4H,t,J=5.0Hz), 3.69(4H,t,J=5.0Hz), 3.85(3H,s), 6.65(1H,s), 7.02(2H,m), 7.24(1H,m),

30 7.39(1H,d,J=4.0Hz), 7.92(1H,s)

Example 177

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3-chlorophenyl) piperazine:

35 Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(3-chlorophenyl)piperazine were reacted by the same way with the

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example 170 to obtain the titled compound.

yield : 84%

m.p. : 75-76°C

¹H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.22(3H,s), 3.27(4H,t,J=5.0Hz),
5 3.68(4H,t,J=5.0Hz), 3.85(3H,s), 6.65(1H,s), 6.90(3H,m), 7.21(1H,t),
7.90(1H,s)

Mass(EI) m/z : Calcd for C₂₀H₂₄N₃O₂Cl₁ 373.1557, found 373.1590

Example 178

10 1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(2-hydroxyphenyl)
piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and

1-(2-hydroxyphenyl)piperazine were reacted by the same way with the
example 170 to obtain the titled compound.

15 yield : 87%

m.p. : 197-199°C

¹H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.21(3H,s), 2.98(4H,t), 3.72(4H,t),
3.84(3H,s), 6.65(1H,s), 6.89(1H,t), 7.00(2H,m), 7.13(2H,m), 7.89(1H,s)

20 Example 179

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3-hydroxyphenyl)
piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and

1-(3-hydroxyphenyl) were reacted by the same way with the example
25 170 to obtain the titled compound.

yield : 88%

m.p. : 177-178°C

¹H NMR(500MHz, CDCl₃): δ 2.19(3H,s), 2.21(3H,s), 3.24(4H,t), 3.68(4H,t),
3.85(3H,s), 6.41(3H,m), 6.65(1H,s), 6.98(1H,s), 7.13(1H,t), 7.88(1H,s)

30

Example 180

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3-thiophenyl)
piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and

35 1-(3-thiophenyl)piperazine were reacted by the same way with the
example 170 to obtain the titled compound.

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yield: 79%

m.p.: 108-110°C

¹H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.21(3H,s), 3.26(4H,t), 3.65(4H,t), 3.84(3H,s), 6.64(1H,s), 6.97(4H,m), 7.05(1H,s), 7.89(1H,s)

5

Example 181

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(2-acetoxyphenyl) piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and

10 1-(2-acetoxyphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.

yield: 84%

m.p.: 129-131°C

15 ¹H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.21(3H,s), 2.32(3H,s), 3.05(4H,t), 3.63(4H,t), 3.85(3H,s), 6.64(1H,s), 6.99(1H,s), 7.04(1H,m), 7.17(2H,m), 7.22(1H,m), 7.90(1H,s)

Example 182

20 1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3-acetoxyphenyl) piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and

1-(3-acetoxyphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.

yield: 87%

25 m.p.: 154-156°C

¹H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.21(3H,s), 2.29(3H,s), 3.27(4H,t), 3.68(4H,t), 3.85(3H,s), 6.64(1H,s), 6.66(2H,m), 6.82(1H,m), 6.98(1H,s), 7.90(1H,s)

30 Example 183

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(2-methoxyphenyl) piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and

35 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.

yield: 90%

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m.p.: 144-145°C

¹H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.22(3H,s), 2.26(3H,s), 2.95(4H,t, J=5.0Hz), 3.65(4H,t,J=5.0Hz), 3.78(3H,s), 3.85(3H,s), 6.59(1H,s), 6.65(1H,s), 7.00(1H,s), 7.11(1H,s), 7.93(1H,s)

5

Example 184

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(5-methoxy-2-methylphenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and

10 1-(5-methoxy-2-methylphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.

yield: 88%

m.p.: 140-141°C

¹H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.22(3H,s), 2.26(3H,s), 2.95(4H,t, J=5.0Hz), 3.65(4H,t,J=5.0Hz), 3.78(3H,s), 3.85(3H,s), 6.59(1H,s), 6.65(1H,s),
15 7.00(1H,s), 7.11(1H,s), 7.93(1H,s)

Example 185

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(2-methoxy-5-methylphenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and

1-(2-methoxy-5-methylphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.

yield: 80%

25 m.p.: 107-108°C

¹H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.21(3H,s), 2.29(3H,s), 3.10(4H,t, J=5.0Hz), 3.69(4H,t,J=5.0Hz), 3.85(3H,s), 3.86(3H,s), 6.55(1H,s), 6.79(2H,m),
7.01(1H,s), 9.94(1H,s)

30 Example 186

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(2-methoxy-5-phenylphenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and

1-(2-methoxy-5-phenylphenyl)piperazine were reacted by the same way
35 with the example 170 to obtain the titled compound.

yield: 91%

m.p.: 139-140°C

¹H NMR(500MHz, CDCl₃): δ 2.21(3H,s), 2.22(3H,s), 3.20(4H,t), 3.74(4H,t), 3.85(3H,s), 3.94(3H,s), 6.65(1H,s), 7.02(2H,m), 7.32(2H,m), 7.42(2H,t), 7.55(2H,d), 7.93(1H,s)

5

Example 187

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(2-isopropenyl phenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and

10 1-(2-isopropenylphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.

yield: 80%

m.p.: 134-135°C

¹H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.21(6H,s), 3.10(4H,t), 3.64(4H,t),
15 3.85(3H,s), 5.08(1H,s), 5.14(1H,s), 6.64(1H,s), 7.05(3H,m), 7.70(1H,m), 7.92(1H,s)

Example 188

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(1-naphthyl)
20 piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and

1-(1-naphthyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.

yield: 92%

25 m.p.: 160-162°C

¹H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.24(3H,s), 3.31(4H,t,J=5.0Hz), 3.83(3H,s), 4.04(4H,t), 6.39(2H,m), 6.69(1H,s), 7.13(1H,t), 7.30(1H,s), 7.46(1H,s)

30 Example 189

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(1-anthranyl) piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and

1-(1-anthranyl)piperazine were reacted by the same way with the
35 example 170 to obtain the titled compound.

yield: 94%

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m.p.: 74-75°C

¹H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.22(3H,s), 3.24(4H,t), 3.70(4H,t), 3.86(3H,s), 6.70(1H,s), 7.05(3H,m), 7.45(5H,m), 8.00(2H,m)

5 Example 190

1-[N-(4,5-Dimethyl-2-methoxyphenyl)-N-methylaminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

- 1-[(4,5-dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine(0.2g, 0.5mmole) was dissolved in
10 dimethylformamide(15ml), sodium hydride(12mg, 0.5mmole) was added thereto slowly, and then the resulting mixture was stirred at room temperature for 15 min, then followed by addition of iodomethane(71mg, 0.5mmole) and subsequently at room temperature for 16 hours. The
15 resulting mixture was concentrated under the reduced pressure to remove the used solvent, extracted with methylene chloride, dried, filtered and purified by column chromatography to obtain the titled compound.

yield: 92%

m.p.: 86-88°C

- 20 ¹H NMR(500MHz, CDCl₃): δ 2.21(3H,s), 2.24(3H,s), 2.92(4H,t), 3.06(3H,s), 3.31(4H,t), 3.75(6H,s), 3.83(3H,s), 6.00(3H,m), 6.71(1H,s), 6.83(1H,s)

Mass(EI) m/z : Calcd for C₂₃H₃₁N₃O₄ 413.2314, found 413.2293

25 Example 191

1-[N-(4,5-Dimethyl-2-methoxyphenyl)-N-methylaminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

- 1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 190
30 to obtain the titled compound.

yield: 90%

m.p.: 137-138°C

¹H NMR(500MHz, CDCl₃): δ 2.15(3H,s), 2.24(9H,s), 2.88(4H,t), 3.06(3H,s), 3.29(4H,t), 3.83(3H,s), 6.45(3H,m), 6.71(1H,s), 6.83(1H,s)

- 35 Mass(EI) m/z : Calcd for C₂₃H₂₉N₃O₂ 381.2416, 381.2436

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Example 192

1-[N-(4,5-Dimethyl-2-methoxyphenyl)-N-methylaminocarbonyl]-4-(3,5-difluorophenyl)piperazine:

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-difluorophenyl)

5 piperazine was reacted by the same way with the example 190 to obtain the titled compound.

yield: 87%

m.p.: 98-100°C

¹H NMR(500MHz, CDCl₃): δ 2.16(3H,s), 2.25(3H,s), 2.92(4H,t),
10 3.06(3H,s), 3.29(4H,t), 3.83(3H,s), 6.23(3H,m), 6.72(1H,s), 6.83(1H,s)

Example 193

1-[N-Ethyl-N-(4,5-dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

15 1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine(0.2g, 0.5mmole) was dissolved in dimethylformamide(15ml), and thereto sodium hydride(12mg, 0.5mmole) was added slowly. The resulting mixture was stirred at room temperature for 15 min. After iodoethane(78mg, 0.5mmol) was added, the resulting mixture was stirred
20 at room temperature for 16 hours. The resulting mixture was concentrated under the reduced pressure to remove the used solvent, extracted with methylene chloride, dried, filtered and purified by column chromatography to obtain the titled compound.

yield: 89%

25 m.p.: oil phase

¹H NMR(500MHz, CDCl₃): δ 1.09(3H,t), 2.16(3H,s), 2.24(3H,s), 2.75(4H,t),
3.28(4H,t), 3.52(2H,q), 3.75(6H,s), 3.81(3H,s), 5.98(3H,m), 6.70(1H,s),
6.80(1H,s)

30 Example 194

1-[N-(4,5-Dimethyl-2-methoxyphenyl)-N-ethylaminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 193
35 to obtain the titled compound.

yield: 93%

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m.p.: 80-82°C

¹H NMR(500MHz, CDCl₃): δ 1.21(3H,t), 2.15(3H,s), 2.23(9H,s), 2.90(4H,t), 3.25(4H,t), 3.59(2H,q), 3.81(3H,s), 6.45(3H,m), 6.69(1H,s), 6.81(1H,s)

5 Example 195

1-[N-(4,5-Dimethyl-2-methoxyphenyl)-N-ethylaminocarbonyl]-4-(3,5-difluorophenyl)piperazine:

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-difluorophenyl)piperazine was reacted by the same way with the example 193 to

10 obtain the titled compound.

yield: 87%

m.p.: oil phase

¹H NMR(500MHz, CDCl₃): δ 1.09(3H,t), 2.16(3H,s), 2.25(3H,s), 2.90(4H,t), 3.27(4H,t), 3.52(2H,q), 3.81(3H,s), 6.24(3H,m), 6.70(1H,s), 6.81(1H,s)

15

Example 196

1-[N-Isopropyl-N-(4,5-dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-difluorophenyl)piperazine:

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-difluorophenyl)

20 piperazine(0.2g, 0.52mmole) was dissolved in dimethylformamide(15ml) and thereto sodium hydride(12.48mg, 0.52mmole) was slowly added. The resulting mixture was stirred at room temperature for 15 min. After 2-iodopropane(87.88mg, 0.52mmole) was added thereto, the resulting mixture was stirred at room temperature for 16 hours. The resulting

25 mixture was concentrated under the reduced pressure to remove the used solvent, extracted with methylene chloride, dried, filtered and purified by column chromatography to obtain the titled compound.

yield: 84%

m.p.: oil phase

30 ¹H NMR(500MHz, CDCl₃): δ 1.10(3H,s), 1.26(3H,s), 2.20(3H,s), 2.25(3H,s), 2.86(4H,t), 3.26(4H,t), 3.77(3H,s), 4.25(1H,m), 6.17(3H,m), 6.68(1H,s), 6.82(1H,s)

Example 197

35 1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

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(a) Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate:

To 3,4-dimethyl-2-methoxyaniline(4.50g, 0.03mol), methylene chloride(100ml) was added and then phenyl chlorothionoformate(5.16g, 0.03mol) was added slowly. The resulting mixture was stirred for 2 hours, and thereto water(150ml) was added. The resulting mixture was extracted with methylene chloride and purified by column chromatography to obtain the titled compound.

yield: 92%

¹H NMR(500MHz, CDCl₃): δ 2.21(3H,s), 2.25(3H,s), 3.85(3H,s), 6.80(1H,s), 6.93(5H,m), 7.31(1H,s)

(b) 1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate(0.2g, 0.7mmol) and 1-(3,5-dimethoxyphenyl)piperazine(0.16g, 0.7mmol) were dissolved in tetrahydrofuran(10ml) and thereto DBU(0.11g, 0.7mmole) was added, followed by stirring at room temperature for 2 hours. The resulting product was concentrated and purified by chromatography to obtain the titled compound.

yield: 84%

m.p.: 128-129°C

¹H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.24(3H,s), 2.32(6H,s), 3.37(4H,t), 3.83(3H,s), 4.08(4H,t), 6.69(3H,m), 7.39(1H,m), 7.47(1H,s)

Mass(EI) m/z : Calcd for C₂₂H₂₉N₃O₃S₁ 415.1929, found 415.1912

Example 198

1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.

yield : 90%

m.p.: 164-165°C

¹H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.24(3H,s), 2.32(6H,s), 3.37(4H,t), 3.83(3H,s), 4.08(4H,t), 6.69(3H,m), 7.39(1H,m), 7.47(1H,s)

Mass(EI) m/z : Calcd for C₂₂H₂₉N₃O₁S₁ 383.2031, found 383.2086

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Example 199

1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(2,3-dimethylphenyl)piperazine:

- Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and
5 1-(2,3-dimethylphenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.
yield: 89%

m.p.: 151-152°C

- ¹H NMR(500MHz, CDCl₃): δ 2.21(3H,s), 2.24(3H,s), 2.29(6H,s),
10 3.03(4H,t), 3.83(3H,s), 4.10(4H,t), 6.69(1H,s), 6.97(2H,m), 7.11(1H,t)

Example 200

1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(3,5-difluorophenyl)piperazine:

- 15 Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(3,5-difluorophenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.
yield : 92%

m.p.: 167-168°C

- 20 ¹H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.24(3H,s), 2.27(3H,s), 2.32(3H,s), 3.39(4H,t,J=5.0Hz), 3.83(3H,s), 4.14(4H,t), 6.70(1H,s), 6.80(2H,m), 7.36(1H,s), 7.44(1H,s)

Example 201

- 25 1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(3,5-dichlorophenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(3,5-dichlorophenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.

- 30 yield: 85%

m.p.: 188-189°C

¹H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.24(3H,s), 3.35(4H,t,J=5.0Hz), 3.83(3H,s), 4.04(4H,t,J=5.0Hz), 6.70(2H,m), 6.83(1H,s), 7.30(1H,s), 7.48(1H,s)

- 35 Mass(EI) m/z : Calcd for C₂₀H₂₄N₃O₂Cl₂ 423.0938, 423.0956

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Example 202

1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(2-fluorophenyl)
piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and

- 5 1-(2-fluorophenyl)piperazine were reacted by the same way with the
example 197 to obtain the titled compound.

yield: 87%

m.p.: 139-140°C

- ¹H NMR(500MHz, CDCl₃): δ 2.21(3H,s), 2.24(3H,s), 3.40(4H,t),
10 3.83(3H,s), 4.25(4H,t), 6.70(1H,s), 7.13(3H,m), 7.37(2H,m)

Example 203

1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(2-chlorophenyl)
piperazine:

- 15 Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and
1-(2-chlorophenyl)piperazine were reacted by the same way with the
example 197 to obtain the titled compound.

yield: 85%

m.p.: 115-116°C

- ¹H NMR(500MHz, CDCl₃): δ 2.21(3H,s), 2.24(3H,s), 3.18(4H,t),
20 3.83(3H,s), 4.09(4H,t), 6.69(1H,s), 7.05(2H,m), 7.33(1H,s), 7.41(2H,m)

Example 204

1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-
25 (2-methoxyphenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and

1-(2-methoxyphenyl)piperazine were reacted by the same way with the
example 197 to obtain the titled compound.

yield: 90%

- 30 m.p.: oil phase

¹H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.23(3H,s), 3.14(4H,t,J=5.0Hz),
3.82(3H,s), 3.88(3H,s), 4.06(4H,t,J=5.0Hz), 6.69(1H,s), 6.94(3H,m),
7.30(1H,s), 7.40(1H,s)

- 35 Example 205

1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-

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(2-methylthiophenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(2-methylthiophenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.

5 yield: 93%

 m.p.: 136-137°C

¹H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.26(3H,s), 2.45(3H,s),
 3.33(4H,t), 3.82(3H,s), 4.39(4H,t), 6.74(1H,s), 7.16(3H,m), 7.47(2H,m)

10 Example 206

 1-[(4,5-Dimethyl-2-methoxyphenyl)aminothi carbonyl]-4-(3-hydroxyphenyl)piperazine:

 Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(3-hydroxyphenyl)piperazine were reacted by the same way with the
15 example 197 to obtain the titled compound.

 yield: 77%

 m.p.: Decomposed(200°C)

¹H NMR(500MHz, CDCl₃): δ 2.17(3H,s), 2.23(3H,s), 3.31(4H,t),
 3.82(3H,s), 4.03(3H,t), 6.37(2H,m), 6.47(1H,d), 6.69(1H,s), 7.13(1H,t),
20 7.45(1H,s)

 Example 207

 1-[(4,5-Dimethyl-2-methoxyphenyl)aminothi carbonyl]-4-(2-phenoxyphenyl)piperazine:

25 Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(2-phenoxyphenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.

 yield: 86%

 m.p.: oil phase

30 ¹H NMR(500MHz, CDCl₃): δ 2.17(3H,s), 2.24(3H,s), 3.19(4H,t),
 3.80(3H,s), 3.85(4H,t), 6.66(1H,s), 6.91(2H,m), 6.98(1H,m), 7.05(3H,m),
 7.13(1H,m), 7.23(1H,m), 7.31(2H,m), 7.36(1H,s)

 Example 208

35 1-[(4,5-Dimethyl-2-methoxyphenyl)aminothi carbonyl]-4-(2-isopropenylphenyl)piperazine:

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Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(2-isopropenylphenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.

yield: 75%

5 m.p.: 157-158°C

¹H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.21(3H,s), 2.24(3H,s), 3.19(4H,t), 3.82(3H,s), 4.05(4H,t), 5.07(1H,s), 5.16(1H,s), 6.69(1H,s), 7.11(3H,m), 7.33(1H,s), 7.45(1H,s)

10 Example 209

1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(2-methoxy-5-methylphenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(2-methoxy-5-methylphenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.

yield: 87%

m.p.: oil phase

¹H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.23(3H,s), 2.29(3H,s), 3.13(4H,t), 3.83(3H,s), 3.85(3H,s), 4.05(4H,t), 6.69(1H,s), 6.83(2H,m), 7.30(1H,s), 7.40(1H,s)

Example 210

1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(1-naphthyl)piperazine:

25 Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(1-naphthyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.

yield: 87%

m.p.: 139-140°C

30 ¹H NMR(500MHz, CDCl₃): δ 2.23(3H,s), 2.24(3H,s), 3.21(4H,t), 3.84(3H,s), 4.09(4H,t), 6.70(1H,s), 7.10(1H,d), 7.48(5H,m), 7.85(1H,m), 8.22(1H,d)

Example 211

35 1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

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Phenyl N-(5-acetyl-2-methoxy-4-methylphenyl)carbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.

yield: 91%

5 m.p.: 103-105°C

¹H NMR(500MHz, CDCl₃): δ 2.54(3H,s), 2.59(3H,s), 3.27(4H,t), 3.70(4H,t), 3.79(6H,s), 3.94(3H,s), 6.13(3H,m), 6.70(1H,s), 7.05(1H,s), 8.72(1H,s)

Example 212

10 1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-(5-acetyl-2-methoxy-4-methylphenyl)carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.

15 yield : 88%

m.p.: 140-142°C

¹H NMR(500MHz, CDCl₃): δ 2.30(3H,s), 2.54(3H,s), 2.59(3H,s), 3.26(4H,t), 3.70(4H,t), 3.97(3H,s), 6.61(3H,m), 6.70(1H,s), 7.06(1H,s), 8.72(1H,s)

20

Example 213

1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminocarbonyl]-4-(3,5-dichlorophenyl)piperazine:

Phenyl N-(5-acetyl-2-methoxy-4-methylphenyl)carbamate and

25 1-(3,5-dichlorophenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.

yield: 78%

m.p.: 170-172°C

30 ¹H NMR(500MHz, CDCl₃): δ 2.54(3H,s), 2.59(3H,s), 3.32(4H,t), 3.74(4H,t), 3.94(3H,s), 6.69(1H,s), 6.86(3H,m), 7.04(1H,s), 8.69(1H,s)

Example 214

1-[(5-(1-Hydroxyethyl)-2-methoxy-4-methylphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

35 1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine(0.2g, 0.47mmol) was dissolved in

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anhydrous ethanol(15ml), and sodium borohydride(17mg) was added thereto, and then the resulting mixture was stirred at room temperature for 2 hours, concentrated under the reduced pressure to remove ethanol, and purified by column chromatography(ethylacetate:hexane = 1:2) to
5 obtain the titled compound.
yield: 96%
m.p.: 152-154°C
¹H NMR(500MHz, CDCl₃): δ 1.41(3H,d), 2.32(3H,s), 3.27(4H,t),
3.71(4H,t), 3.79(6H,s), 3.87(3H,s), 5.04(1H,q), 6.10(3H,m), 6.63(1H,s),
10 7.01(1H,s), 8.22(1H,s)

Example 215

1-([5-(1-Hydroxyethyl)-2-methoxy-4-methylphenyl]aminocarbonyl)-4-(3,5-dimethylphenyl)piperazine:
15 1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 214 to obtain the titled compound.
yield: 96%
m.p.: 140-142°C
20 ¹H NMR(500MHz, CDCl₃): δ 1.48(3H,d), 2.33(3H,s), 3.26(4H,t),
3.68(4H,t), 3.87(3H,s), 5.06(1H,q), 6.61(3H,m), 6.64(1H,s), 7.01(1H,s),
8.22(1H,s)

Example 216

25 1-[(2-Methoxy-4-methyl-5-vinylphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
1-([5-(1-Hydroxyethyl)-2-methoxy-4-methylphenyl]aminocarbonyl)-4-(3,5-dimethoxyphenyl)piperazine(0.2g, 0.47mmol) was dissolved in chloroform(15ml), pyridium p-toluenesulfonate(0.12g, 0.47mmol) was
30 added thereto, and the resulting mixture was refluxed for 16 hours, and concentrated under the reduced pressure to remove chloroform and purified by column chromatography(ethylacetate:hexane=1:2) to obtain the titled compound.
yield: 84%
35 m.p.: 163-165°C
¹H NMR(500MHz, CDCl₃): δ 2.31(3H,s), 3.23(4H,t), 3.58(4H,t), 3.77(6H,s),

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3.87(3H,s), 5.20(1H,d), 5.62(1H,d), 6.59(3H,m), 6.63(1H,s), 6.88(1H,t),
6.99(1H,s), 8.32(1H,s)

Example 217

5 1-[(2-Methoxy-4-methyl-5-vinylphenyl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[[5-(1-Hydroxyethyl)-2-methoxy-4-methylphenyl]aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 216 to obtain the titled compound.

10 yield: 82%

m.p.: 201-203°C

¹H NMR(500MHz, CDCl₃): δ 2.29(6H,s), 2.34(3H,s), 3.24(4H,t), 3.68(4H,t),
3.87(3H,s), 5.22(1H,d), 5.66(1H,d), 6.59(3H,m), 6.63(1H,s), 6.86(1H,t),
7.02(1H,s), 8.32(1H,s)

15

Example 218

1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(5-acetyl-2-methoxy-4-methylphenyl)thiocarbamate and
20 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.

yield: 82%

m.p.: 163-165°C

¹H NMR(500MHz, CDCl₃): δ 2.16(3H,s), 2.56(3H,s), 3.35(4H,t),
25 3.91(6H,s), 4.03(3H,s), 4.13(4H,t), 6.06(3H,m), 6.73(1H,s), 8.62(1H,s)

Example 219

1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminothiocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

30 Phenyl N-(5-acetyl-2-methoxy-4-methylphenyl)thiocarbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.

yield: 79%

m.p.: 180-182°C

¹H NMR(500MHz, CDCl₃): δ 2.29(6H,s), 2.57(6H,s), 3.32(4H,t),
35 3.92(3H,s), 4.12(4H,t), 6.56(3H,m), 6.72(1H,s), 7.39(1H,s), 8.63(1H,s)

Example 220

1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminothiocarbonyl]-4-(3,5-dichlorophenyl)piperazine:

- 5 Phenyl N-(5-acetyl-2-methoxy-4-methylphenyl)thiocarbamate and 1-(3,5-dichlorophenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.

yield: 79%

m.p.: 201-203°C

- 10 ¹H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.57(3H,s), 3.46(4H,t), 3.92(3H,s), 4.25(4H,t), 6.64(1H,s), 6.88(3H,m), 7.72(1H,s), 8.57(1H,s)

Example 221

1-[(5-(1-Hydroxyethyl)-2-methoxy-4-methylphenyl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

- 15 1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 214 to obtain the titled compound.

yield: 94%

- 20 m.p.: 146-148°C

¹H NMR(500MHz, CDCl₃): δ 1.44(3H,d), 2.32(3H,s), 3.35(4H,t), 3.78(6H,s), 3.84(3H,s), 4.11(4H,t), 5.06(1H,q), 6.13(3H,m), 6.66(1H,s), 7.41(1H,s), 7.77(1H,s)

25 Example 222

1-[(5-(1-Hydroxyethyl)-2-methoxy-4-methylphenyl)aminothiocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

- 1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminothiocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the
30 example 214 to obtain the titled compound.

yield: 93%

m.p.: 150-152°C

- 35 ¹H NMR(500MHz, CDCl₃): δ 1.44(3H,d), 2.29(6H,s), 2.32(3H,s), 3.30(4H,t), 3.84(3H,s), 4.07(4H,t), 5.06(1H,q), 6.61(3H,m), 6.66(1H,s), 7.38(1H,s), 7.79(1H,s)

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Example 223

1-([5-(1-Hydroxyethyl)-2-methoxy-4-methylphenyl]aminothiocarbonyl)-4-(3,5-dichlorophenyl)piperazine:

1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminothiocarbonyl]-4-

- 5 (3,5-dichlorophenyl)piperazine was reacted by the same way with the example 214 to obtain the titled compound.

yield: 77%

m.p.: 166-168°C

- ¹H NMR(500MHz, CDCl₃): δ 1.45(3H,d), 2.33(3H,s), 3.35(4H,t),
10 3.84(3H,s), 4.03(4H,t), 5.07(1H,q), 6.68(3H,m), 6.83(1H,s), 7.37(1H,s),
7.82(1H,s)

Example 224

- Ethyl 2-([4-(3,5-dimethoxyphenyl)piperazino]carbonyl)-2-methoxy-4,5-
15 dimethylanilino)acetate :

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine(0.2g, 0.5mmol) was dissolved in dimethylformamide(15ml), sodium hydride(18.5mg, 0.5mmol) was added thereto, and the resulting mixture was stirred at room temperature.

- 20 Then, ethyl bromoacetate(83.5mg, 0.5mmol) was added thereto and the resulting mixture was stirred for 3 hours, concentrated under the reduced pressure to remove the used solvent and purified by column chromatography(ethylacetate:hexane=1:2) to obtain the titled compound.
yield: 79%

- 25 m.p.: oil phase

¹H NMR(500MHz, CDCl₃): δ 1.36(3H,t), 2.15(3H,s), 2.23(3H,s), 2.91(4H,t),
3.22(4H,t), 3.82(6H,s), 4.12(3H,s), 4.18(2H,s), 5.98(3H,m), 6.69(1H,s),
7.03(1H,s)

- 30 Example 225

Ethyl 2-([4-(3,5-dimethylphenyl)piperazino]carbonyl)-2-methoxy-4,5-dimethylanilino)acetate :

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-

- (3,5-dimethylphenyl)piperazine was reacted by the same way with the
35 example 224 to obtain the titled compound.

yield: 78%

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m.p.: oil phase

¹H NMR(500MHz, CDCl₃): δ 1.26(3H,t), 1.56(6H,s), 2.17(3H,s), 2.24(3H,s), 3.32(4H,t), 3.52(4H,t), 3.82(3H,s), 4.15(2H,q), 4.18(2H,s), 6.70(3H,m), 6.94(1H,s), 7.46(1H,s)

5

Example 226

2-([4-(3,5-Dimethoxyphenyl)piperazino]carbonyl)-2-methoxy-4,5-dimethylanilino)acetic acid:

10 Ethyl 2-([4-(3,5-dimethoxyphenyl)piperazino]carbonyl)-2-methoxy-4,5-dimethylanilino)acetate(200mg, 0.41mmole) was dissolved in dioxane:distilled water(4:1, 15ml), lithium hydroxide monohydrate(50.7mg, 1.23mmol) was added thereto, and then the resulting mixture was stirred at room temperature for 3 hours, acidified with 1N-hydrochloric acid, extracted with ethylacetate, filtered to dryness, concentrated under
15 the reduced pressure to remove the used solvent, and purified by column chromatography(ethylacetate:hexane=1:2) to obtain the titled compound.

yield: 80%

m.p.: 188-189°C

20 ¹H NMR(500MHz, CDCl₃): δ 2.14(3H,s), 2.23(3H,s), 2.93(4H,t), 3.35(4H,t), 3.75(6H,s), 3.87(3H,s), 4.18(2H,s), 5.96(3H,m), 6.71(1H,s), 7.71(1H,s)

Example 227

25 2-([4-(3,5-Dimethylphenyl)piperazino]carbonyl)-2-methoxy-4,5-dimethylanilino)acetic acid:

Ethyl 2-([4-(3,5-dimethylphenyl)piperazino]carbonyl)-2-methoxy-4,5-dimethylanilino)acetate was reacted by the same way with the example 226 to obtain the titled compound.

yield: 78%

30 m.p.: 170-171°C

¹H NMR(500MHz, CDCl₃): δ 2.13(3H,s), 2.24(9H,s), 2.91(4H,t), 3.35(4H,t), 3.83(3H,s), 4.18(2H,s), 6.45(3H,m), 6.70(2H,s), 6.80(1H,s)

Example 228

35 1-[(2-Hydroxy-4,5-dimethylphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

(a) 4,5-Dimethyl-2-nitrophenol:

- To 3,4-dimethylphenol(12.1g, 0.1mol), trifluoroacetic acid(250ml) was added, and in water bath sodium nitrite(12.4g, 0.18mol) was added
5 slowly. The resulting mixture was stirred at room temperature for 14 hours and concentrated under the reduced pressure to remove trifluoroacetic acid, followed by addition of water(150ml), extracted with ether and purified by column chromatography to obtain the titled compound.
10 yield: 80%
¹H NMR(500MHz, CDCl₃): δ 2.23(3H,s), 2.29(3H,s), 6.93(1H,s), 7.84(1H,s)

(b) 4,5-Dimethyl-2-hydroxyaniline:

- 15 To 4,5-dimethyl-2-nitrophenol(11.7g, 0.07mol), tetrahydrofuran(100ml) and ethanol(40ml) were added, and 10% palladium/activated carbon(0.57g) was added slowly, and then the mixture was hydrogenated for 5 hours. The reaction mixture was concentrated and chromatographed by the same way above to obtain the titled compound.
20 yield : 77%
¹H NMR(500MHz, CDCl₃): δ 2.11(6H,s), 6.56(2H,s)

(c) Phenyl N-(4,5-dimethyl-2-hydroxyphenyl)carbamate:

- To 4,5-dimethyl-2-hydroxyaniline(6.80g, 0.05mole), methylene
25 chloride(100ml) was added and then phenyl chloroformate(8.0g, 0.05mole) was added slowly. After stirring for 2 hours, addition of water(150ml), extraction with methylene chloride and column chromatography gave the titled compound.
yield: 92%
30 ¹H NMR(500MHz, CDCl₃): δ 2.17(6H,s), 6.74(1H,s), 7.15(5H,m), 7.31(1H,s)

(d) Phenyl N-[2-(t-butyldimethylsilyloxy)-4,5-dimethylphenyl]carbamate:

- To a mixture of phenyl N-(4,5-dimethyl-2-hydroxyphenyl)carbamate
35 (7.72g, 0.03mol) and imidazole(2.2g, 33mmol), methylene chloride(100ml) was added, and with stirring t-butyldimethylsilylchloride(5.0g, 33mmole)

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was added. Then the mixture was stirred for 2 hours, and water(150ml) was added thereto. The resulting mixture was extracted with methylene chloride, dried, concentrated under the reduced pressure and purified by column chromatography to obtain the titled compound.

5 yield: 83%

^1H NMR(500MHz, CDCl_3): δ 0.27(6H,s), 0.98(9H,s), 2.17(6H,s), 7.12(5H,m), 7.30(2H,s)

(e) 1-[(2-Hydroxy-4,5-dimethylphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

10 Phenyl N-[2-(t-butyldimethylsilyloxy)-4,5-dimethylphenyl]carbamate (0.17g, 0.5mmole) and 1-(3,5-dimethoxyphenyl)piperazine(0.13g, 0.6mmole) were dissolved in tetrahydrofuran(10ml), and thereto with stirring DBU(0.09g, 0.6mmole) was added, and the resulting mixture
15 was stirred for 2 hours, concentrated and chromatographed to obtain the titled compound.

yield: 87%

m.p.: 145-146°C

^1H NMR(500MHz, CDCl_3): δ 2.14(3H,s), 2.18(3H,s), 3.26(4H,t), 3.67(4H,t),
20 3.79(6H,s), 6.07(3H,m), 6.40(3H,m), 6.67(1H,s), 6.82(1H,s), 8.87(1H,s)

Example 229

1-[(2-Hydroxy-4,5-dimethylphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
25 Phenyl N-[2-hydroxy-4,5-dimethylphenyl]carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 228 to obtain the titled compound.

yield: 84%

m.p.: 160-162°C

^1H NMR(500MHz, CDCl_3): δ 2.13(3H,s), 2.17(3H,s), 2.31(6H,s),
30 3.26(4H,t), 3.75(4H,t), 6.73(3H,m), 6.81(1H,s), 8.86(1H,s)

Example 230

1-[(2-Hydroxy-4,5-dimethylphenyl)aminocarbonyl]-4-(3,5-difluorophenyl)
35 piperazine:
Phenyl N-[2-hydroxy-4,5-dimethylphenyl]carbamate and

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1-(3,5-difluorophenyl)piperazine were reacted by the same way with the example 228 to obtain the titled compound.

yield: 80%

m.p.: 152-154°C

- 5 ¹H NMR(500MHz, CDCl₃): δ 2.17(3H,s), 2.20(3H,s), 3.30(4H,t), 3.70(4H,t), 6.40(3H,m), 6.70(1H,s), 6.82(1H,s), 6.98(1H,s)

Example 231

- 10 1-[(2-hydroxy-4,5-dimethylphenyl)aminocarbonyl]-4-(3,5-dichlorophenyl) piperazine:

Phenyl N-(2-hydroxy-4,5-dimethylphenyl)carbamate and

1-(3,5-dichlorophenyl)piperazine were reacted by the same way with the example 228 to obtain the titled compound.

yield: 77%

- 15 m.p.: oil phase

¹H NMR(500MHz, CDCl₃): δ 2.15(3H,s), 2.20(3H,s), 3.32(4H,t), 3.69(4H,t), 6.29(3H,m), 6.69(1H,s), 6.81(1H,s), 8.65(1H,s)

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Antitumor activities of compounds of the present invention were tested in vitro against 5 kinds of human tumor cell lines and 2 kinds of leukemia tumor cell lines. The method and result of in vitro tests is as follows.

5

Experimental 1 : In vitro antitumor effect against human tumor cell lines.

- 10 A. Tumor cell line : A549 (human non-small lung cell)
SKOV-3 (human ovarian)
HCT-15 (human colon)
XF 498 (human CNS)
SKMEL-2 (human melanoma)

15 B. SRB Assay Method.

a. Human solid tumor cell lines, A549(non-small lung cell), SKMEL-2(melanoma), HCT-15(colon), SKOV-3(ovarian), XF-498(CNS) were cultured at 37°C, in 5% CO₂ incubators using the
20 RPMI 1640 media containing 10% FBS, while they were transfer-cultured successively once or twice per week. Cell cultures were dissolved in a solution of 0.25% trypsin and 3 mM CDTA PBS(-) and then cells were separated from media which the cells were stucked on.

25

b. $5 \times 10^3 \sim 2 \times 10^4$ cells were added into each well of 96-well plate and cultured in 5% CO₂ incubator, at 37°C, for 24 hours.

30 c. Each sample drug was dissolved in a little DMSO and diluted with the used medium to a prescribed concentration for experiments, wherein the final concentration of DMSO was controlled below 0.5%.

35 d. Medium of each well cultured for 24 hours as above b. was removed by aspiration. Each 200 μ l of drug samples prepared in c. was added into each well and the wells were cultured for 48 hours. Tz(time zero) plates were collected at the point of time drugs were added.

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e. According to the SRB assay method, cell fixing with TCA, staining with 0.4% SRB solution, washing with 1% acetic acid and elution of dye with 10mM Tris solution were carried out on Tz plates and culture-ended plates, and then, OD values were measured at 520 nm.

5

C. Calculation of result

a. Time zero(Tz) value was determined with measuring the SRB protein value at the point of time drugs were added.

10

b. Control value(C) was determined with the OD value of an well untreated with drug.

c. Drug-treated test value(T) was determined with the OD value of drug-treated well.

15

d. Effects of drugs were estimated with growth stimulation, net growth inhibition, net killing etc. calculated from Tz, C and T.

e. If $T \geq T_z$, cellular response function was calculated by $100 \times (T - T_z) / (C - T_z)$, and if $T < T_z$, by $100 \times (T - T_z) / T_z$. The results are shown in the next table 1.

20

* REFERENCE

- 25 1) P. Skehan, R. Strong, D. Scudiero, A. Monks, J. B. McMahan, D. T. Vistica, J. Warren, H. Bokesch, S. Kenny and M. R. Boyd : Proc. Am. Assoc. Cancer Res., 30, 612(1989)
- 2) L. V. Rubinstein, R. H. Shoemaker, K. D. Paull, R. M. Simon, S. Tosini, P. Skehan, D. Scudiero, A. Monks and M. R. Boyd. ; J. Natl. Cancer Inst., 82, 1113(1990)
- 30 3) P. Skehan, R. Strong, D. Scudiero, A. Monks, J. B. McMahan, D. T. Vistica, J. Warren, H. Bokesch, S. Kenny and M. R. Boyd. ; J. Natl. Cancer Ins., 82, 1107(1990)

35 D. Results.

It was found that compounds of the present invention have the

superior antitumor activities than those of cisplatin, one control, and equal to or higher antitumor activities than those of adriamycin, another control, against human solid cancer cell lines.

5 Table 1.

ED₅₀= μ g/ml

| Ex. No. | A549 | SK-OV-3 | SK-MEL-2 | XF-498 | HCT 15 |
|---------|--------|---------|----------|--------|--------|
| 4 | 0.007 | 0.022 | 0.007 | 0.94 | 0.093 |
| 5 | 0.71 | 0.96 | 0.60 | >10.0 | 0.96 |
| 9 | 0.15 | 0.07 | 0.21 | 0.11 | 0.11 |
| 11 | 0.91 | 0.56 | 0.62 | 0.73 | 0.71 |
| 14 | 0.022 | 0.02 | 0.001 | 0.16 | 0.007 |
| 15 | 0.002 | 0.05 | 0.052 | 0.035 | 0.038 |
| 16 | 0.008 | 0.04 | 0.038 | 0.005 | 0.061 |
| 17 | 0.018 | 0.01 | 0.021 | 0.077 | 0.008 |
| 22 | 0.0009 | 0.006 | 0.027 | 0.0053 | 0.01 |
| 23 | 0.09 | 0.04 | 0.09 | 0.092 | 0.05 |
| 24 | 0.03 | 0.006 | 0.01 | 0.234 | 0.01 |
| 27 | 0.02 | 0.11 | 0.01 | 0.046 | 0.165 |
| 28 | 0.06 | 0.07 | 0.001 | 0.41 | 0.05 |
| 46 | 0.21 | 0.12 | 0.08 | 0.14 | 0.16 |
| 47 | 0.92 | 0.62 | 0.47 | 0.64 | 0.81 |
| 53 | 0.47 | 0.47 | 0.64 | 0.67 | 0.71 |
| 56 | 0.017 | 0.0027 | 0.01 | 0.013 | 0.045 |
| 57 | 0.27 | 0.15 | 0.18 | 0.22 | 0.25 |
| 63 | 0.04 | 0.1 | 0.11 | 0.03 | 0.07 |
| 64 | 0.42 | 0.56 | 0.52 | 0.23 | 0.37 |
| 73 | 0.01 | 0.0054 | 0.02 | 0.013 | 0.012 |
| 74 | 0.016 | 0.0138 | 0.02 | 0.026 | 0.021 |
| 75 | 0.19 | 0.09 | 0.09 | 0.13 | 0.12 |

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| Ex. No. | A549 | SK-OV-3 | SK-MEL-2 | XF 498 | HCT 15 |
|---------|----------|----------|----------|----------|----------|
| 81 | 0.0032 | 0.0007 | 0.0107 | 0.0097 | 0.0054 |
| 82 | 0.0676 | 0.0249 | 0.0754 | 0.0479 | 0.0346 |
| 5 85 | 0.048 | 0.117 | 0.039 | 0.104 | 0.10 |
| 88 | 0.014 | 0.043 | 0.02 | 0.009 | 0.011 |
| 99 | 0.43 | 0.41 | 0.40 | 0.52 | 0.36 |
| 100 | 4.54 | 3.02 | 3.47 | 0.66 | 4.21 |
| 10 103 | 0.52 | 0.46 | 0.49 | 0.36 | 0.33 |
| 109 | 0.47 | 0.91 | 0.86 | 0.53 | 0.49 |
| 110 | 0.52 | 1.06 | 0.97 | 0.81 | 0.69 |
| 112 | 0.56 | 6.43 | 0.22 | 2.07 | 0.61 |
| 15 128 | 0.40 | 0.37 | 0.42 | 0.44 | 0.51 |
| 132 | 0.03 | 0.01 | 0.03 | 0.04 | 0.04 |
| 133 | 0.57 | 0.94 | 0.53 | 0.61 | 0.57 |
| 134 | 0.0009 | 0.0091 | 0.0086 | 0.002 | 0.0065 |
| 20 135 | 0.056 | 0.092 | 0.102 | 0.06 | 0.066 |
| 140 | 0.33 | 0.47 | 0.56 | 0.54 | 0.49 |
| 142 | 0.015 | 0.011 | 0.021 | 0.026 | 0.017 |
| 143 | 0.0004 | 0.0095 | 0.0121 | 0.0009 | 0.0108 |
| 25 147 | 0.031 | 0.092 | 0.024 | 0.466 | 0.18 |
| 148 | 0.01 | 0.07 | 0.03 | 0.05 | 0.05 |
| 151 | 0.004 | 0.008 | 0.007 | 0.007 | 0.037 |
| 152 | 0.18 | 0.37 | 0.2 | 0.26 | 0.44 |
| 30 156 | 0.06 | 0.10 | 0.09 | 0.06 | 0.07 |
| 157 | 0.000002 | 0.000002 | 0.000043 | 0.000245 | 0.000211 |
| 159 | 0.05 | 0.10 | 0.07 | 0.21 | 0.17 |

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| | | | | | | |
|----|------------|----------|---------|----------|----------|----------|
| | Ex. No. | A549 | SK-OV-3 | SK-MEL-2 | XF 498 | HCT 15 |
| | 171 | 0.000645 | 0.00372 | 0.003233 | 0.000572 | 0.001809 |
| | 172 | 0.0047 | 0.0097 | 0.0233 | 0.0086 | 0.0180 |
| 5 | 174 | 0.54 | 0.56 | 0.27 | 0.49 | 0.33 |
| | 177 | 0.52 | 0.39 | 0.17 | 0.12 | 0.09 |
| | 179 | 1.04 | 0.98 | 0.72 | 0.74 | 0.63 |
| | 183 | 0.42 | 2.27 | 1.17 | 1.41 | 2.09 |
| 10 | 184 | 0.28 | 0.34 | 0.17 | 0.12 | 0.20 |
| | 190 | 0.004 | 0.008 | 0.002 | 0.443 | 0.017 |
| | 191 | 0.09 | 0.28 | 0.06 | 0.47 | 0.40 |
| | 198 | 0.021 | 0.068 | 0.008 | 0.072 | 0.56 |
| 15 | 200 | 0.50 | 0.53 | 0.26 | 1.01 | 0.44 |
| | 201 | 0.014 | 0.053 | 0.049 | 0.026 | 0.071 |
| | 202 | 0.57 | 1.26 | 0.48 | 2.09 | 0.64 |
| | 206 | 0.47 | 0.54 | 0.52 | 0.70 | 0.38 |
| 20 | Cisplatin | 0.8184 | 0.7134 | 0.7147 | 0.7771 | 3.0381 |
| | Adriamycin | 0.0168 | 0.0176 | 0.0108 | 0.0250 | 1.6689 |

25

Experimental 2.**In vitro antitumor effects against animal leukemia cells.****A. Materials :**

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Tumor cell lines : L1210(mouse leukemia cell)**P388 (mouse lymphoid neoplasma cell)****B. Method : Dye Exclusion Assay.**

1) The concentrations of L1210 and P388 cells being cultured in
 35 RPMI 1640 media containing 10% FBS were regulated to 1×10^6
 cells/ml.

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2) Sample drugs of respective concentrations diluted in the ratio of log doses were added into cell media, and cultured at 37°C, for 48 hours, in 50% CO₂ incubator, and then viable cell number was measured by dye exclusion test using trypan blue.

3) The concentration of sample compounds showing 50 % cell growth inhibition(IC₅₀) compared with the control were determined and listed in the table 2 below.

10

* REFERENCE

- 1) P. Skehan, R. Strong, D. Scudiero, A. Monks, J. B. McMahan, D. T. Vistica, J. Warren, H. Bokesch, S. Kenney and M. R. Boyd. : Proc. Am. Assoc. Cancer Res., 30, 612(1989).
- 15 2) L. V. Rubinstein, R. H. Shoemaker, K. D. Paull, R. M. Simon, S. Tosini, P. Skehan, D. Scudiero, A. Monks, J. Natl. Cancer Inst., 82, 1113(1990)
- 3) P. Skehan, R. Strong, D. Scudiero, J. B. McMahan, D. T. Vistica, J. Warren, H. Bokesch, S. Kenney and M. R. Boyd. : J. Natl. Cancer
20 Inst., 82, 1107(1990)

C. Results

As the results of measurement of antitumor activities of compounds of the present invention against L1210 and P388 mouse cancer cells, it was found that the compounds tested have equal to or higher antitumor activities than those of the control drug, mitomycin C.

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| Ex. No. | L1210 | P388 |
|---------|-------|------|
| 8 | 0.9 | 0.4 |
| 12 | 0.2 | - |
| 13 | 0.5 | - |
| 14 | 0.3 | - |
| 15 | 0.3 | 0.4 |
| 16 | 0.5 | 0.3 |
| 17 | 1.2 | 0.8 |
| 24 | 0.5 | 0.5 |
| 49 | 1.5 | - |
| 56 | 0.2 | 0.2 |
| 57 | 1.8 | 1.2 |
| 60 | 1.1 | - |
| 63 | 0.5 | 0.3 |
| 64 | 1.9 | 1.4 |
| 69 | - | 0.5 |
| 71 | - | 0.07 |
| 72 | - | 0.9 |
| 73 | 0.2 | 0.04 |
| 74 | 0.5 | 0.4 |
| 76 | - | 0.4 |
| 77 | - | 0.5 |

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| | Ex. No. | L1210 | P388 |
|----|-----------|-------|------|
| 5 | 132 | 0.4 | 0.4 |
| | 134 | 0.5 | 0.2 |
| | 140 | 1.8 | 1.6 |
| | 143 | 0.5 | 0.4 |
| | 144 | 1.2 | 0.5 |
| 10 | 148 | 1.6 | - |
| | 149 | 1.0 | 0.6 |
| | 151 | - | 1.2 |
| | 152 | 0.3 | 0.3 |
| | 154 | - | 0.1 |
| 15 | 157 | 1.7 | 1.0 |
| | 158 | 0.5 | 0.2 |
| | 170 | 0.4 | 0.4 |
| | 173 | 0.5 | 0.2 |
| | 178 | 1.8 | 1.6 |
| 20 | 181 | 0.5 | 0.4 |
| | 182 | 1.2 | 0.5 |
| | 186 | 1.6 | - |
| | 187 | 1.0 | 0.6 |
| | 190 | 0.3 | 0.3 |
| 25 | 195 | 1.7 | 1.0 |
| | 196 | 0.5 | 0.2 |
| | Mitomycin | 1.6 | 1.1 |

35 Experimental 3.

* In vivo antitumor effects against mouse leukemia P388 cells.

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A. Material of experiment

BDF1 mice were used.

B. Method of experiment

1) Leukemia P388 cells being transfer-cultured successively in
5 DBA/2 mouse, were grafted into each mouse of a group comprising 8
mice of 6 week old BDF1 mouse with the dose of 1×10^6 cells/0.1ml.

2) Sample drugs were dissolved in PBS or suspended in 0.5%
tween 80, and then injected into abdominal cavity of mouse at each
10 prescribed concentration on days 1, 5, 9, respectively.

3) With observation everyday, survival times of tested mice were
measured. Antitumor activities was determined in such a manner that
the increasing ratio(T/C%) of average survival days of drug-treated
15 groups compared with the control group was calculated using the
mean survival times of each tested groups.

The results are shown at the next table 3.

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| | Ex. No. | Dose(mg/kg) | T/C(%) | Interval of administration |
|----|---------|-----------------|-------------------|----------------------------|
| 5 | 8 | 200 | 140.9 | on days 1, 5, 9 |
| | | 100 | 104.5 | |
| | 15 | 25 10 | 150 110 | nine everyday |
| 10 | 16 | 50 | 165 | nine everyday |
| | | 25 | 110 | |
| | 22 | 100 50 25 | 150 140 110 | nine everyday |
| 15 | 56 | 200 | 227.3 | on days 1, 5, 9 |
| | | 100 | 140.9 | |
| | | 50 | 118.2 | |
| 20 | 56 | 50 | 165.0 | nine everyday |
| | | 25 | 145.0 | |
| | | 10 | 140.0 | |
| 25 | 73 | 50 | 180.0 | nine everyday |
| | | 25 | 150.0 | |
| | | 10 | 140.0 | |
| 30 | 74 | 50 | 250.0 | nine everyday |
| | | 25 | 150.0 | |
| | | 10 | 140.0 | |
| 35 | | | | |

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| Ex. No. | Dose(mg/kg) | T/C(%) | Interval of adminstration |
|---------|-------------|--------|------------------------------|
| 5 | 200 | 218.2 | on day 1, 5, 9 |
| | 100 | 145.5 | |
| | 50 | 127.3 | |
| 10 | 50 | 210.0 | nine everyday |
| | 25 | 140.0 | |
| | 10 | 140.0 | |
| 15 | 100 | 127.3 | on days 1, 5, 9 |
| | 50 | 100.0 | |
| | 25 | 100.0 | |
| 20 | 100 | 150.0 | nine everyday |
| | 50 | 110.0 | |
| | 25 | 110.0 | |
| 25 | 100 | 150.0 | nine everyday |
| | 50 | 110.0 | |
| | 25 | 100.0 | |
| 30 | 200 | 125.0 | nine everyday |
| | 100 | 110.0 | |
| | 50 | 110.0 | |
| 35 | 100 | 140.0 | on days 1, 4, 8 |
| | 50 | 100.0 | |
| | 25 | 100.0 | |
| 40 | 200 | 190.9 | on days 1, 4, 8 |
| | 100 | 127.3 | |
| | 50 | 118.2 | |

30

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REFERENCE

A. Goldin et al.: Euro. J. Cancer, 17, 129 (1981).

5 C. Result

Through in vivo experiments using P388 mouse cancer cells, significant antitumor effect of the compounds of examples were observed.

10

Experimental 4.

Acute toxicity test (LD₅₀) : Litchfield-Wilcoxon method.

- 15 6 weeks old ICR mice(male $30 \pm 2.0g$) were fed freely with solid feed and water at room temperature, $23 \pm 1^\circ C$ and at humidity $60 \pm 5\%$. Sample drugs were injected into the abdominal cavities of mice, while each group comprises 6 mice. Observed during 14 days, external appearances and life or dead were recorded, and then, visible
- 20 pathogenies were observed from dead animals by dissection. LD₅₀ value was calculated by Litchfield-wilcoxon method.
- The results are shown at the next table 4.

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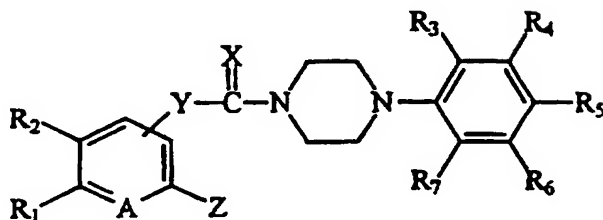
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| | Ex. No. | LD ₅₀ (mg/kg)(i.p) |
|----|-----------|-------------------------------|
| | 8 | 707 |
| 5 | 12 | 165 |
| | 13 | 284.8 |
| | 15 | 190 |
| | 16 | 282.8 |
| 10 | 22 | >2,000 |
| | 28 | >2,000 |
| | 56 | 410 |
| | 57 | 455 |
| 15 | 73 | 250 |
| | 74 | 361.4 |
| | 81 | 1,600 |
| 20 | 82 | 700 |
| | 170 | 573 |
| | 172 | 723 |
| | 182 | 348 |
| 25 | 184 | 309 |
| | 186 | >2,000 |
| | 187 | 417.6 |
| 30 | Cisplatin | 9.7 |

As described above, it was found that the compounds of the present invention are more safer and have superior antitumor activities to cisplatin, and accordingly have solved the problems of drugs by the prior art such as restriction of dosage, toxicity, etc.

What is claimed:

1. A compound of the general formula(I)

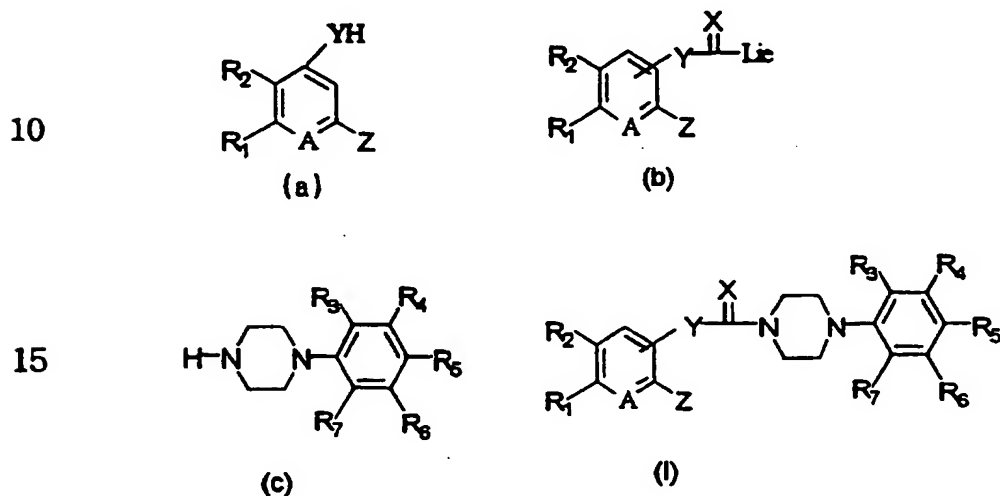


(I)

wherein R_1 and R_2 are independently hydrogen, substituted or unsubstituted C_1 - C_8 alkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted C_2 - C_8 unsaturated alkyl, ketone, substituted or unsubstituted aryl, substituted or unsubstituted C_1 - C_4 alkoxy, substituted or unsubstituted arylhydroxy, substituted or unsubstituted amino, C_1 - C_4 lower ester, C_1 - C_4 lower thioester, thiol, substituted or unsubstituted carboxyl, epoxy, substituted or unsubstituted C_1 - C_4 lower thioalkoxy; or R_1 and R_2 are fused to form C_3 - C_4 saturated or unsaturated chain; R_3 , R_4 , R_5 , R_6 and R_7 are independently hydrogen, halogen, hydroxy, nitro, C_1 - C_4 lower ester, C_1 - C_4 lower alkyl, C_1 - C_4 lower thioalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, C_1 - C_4 lower alkoxy, C_1 - C_4 lower thioalkoxy, substituted or unsubstituted aryl, substituted or unsubstituted lower arylalkoxy, substituted or unsubstituted lower alkylamino, or lower alkyl substituted or unsubstituted carbamate; or among R_3 , R_4 , R_5 , R_6 and R_7 , two adjacent groups are bonded with each other to form 1,2-phenylene or 2,3-naphthylene; X is oxygen, sulfur, or substituted or unsubstituted imino; Y is bonded at the 3-position or 4-position of the aromatic ring part wherein Y is oxygen or $-NR_8$ - (wherein, R_8 is the same with the above-mentioned R_3); Z is hydroxy, C_1 - C_4 lower alkoxy, C_1 - C_4 lower thioalkoxy, substituted or unsubstituted aryloxy, C_1 - C_4 lower alkylamino, substituted or unsubstituted cycloamino containing 1-5 nitrogen atoms; A is nitrogen or $-CH=$; and pharmaceutically acceptable acid addition salts thereof.

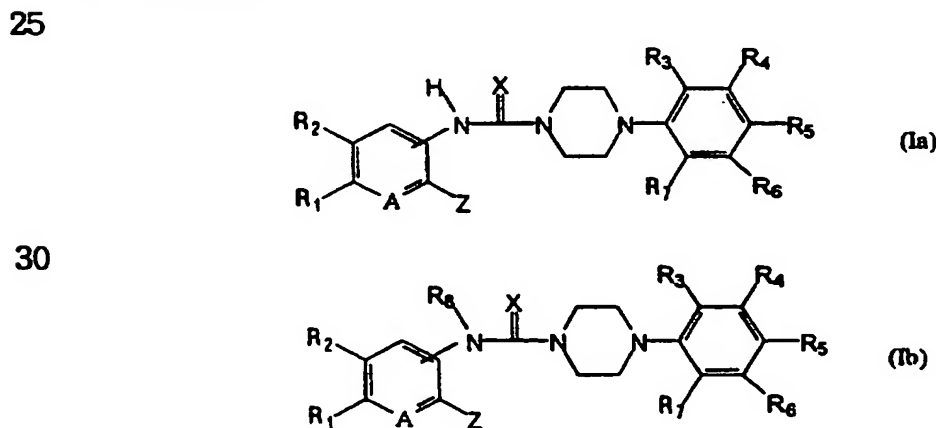
- 120 -

2. A process for the preparation of compound of the general formula(I) or a pharmaceutically acceptable acid addition salt thereof comprising reacting a compound of the general formula(a) with a $-C(=X)-$ group-providing agent in the presence of organic solvent to obtain a
 5 compound of the general formula(b) and reacting the compound of the general formula(b) with a compound of the general formula(c).



20 wherein, R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , A, X, Y and Z are as defined above and Lie is a leaving group.

3. A process for the preparation of compound of the general formula(Ib) by introducing R_8 providing agent into a compound of the general formula(Ia).



35 wherein, R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , A, X and Z are as defined above.

INTERNATIONAL SEARCH REPORT

International application N .

PCT/KR 97/00128

A. CLASSIFICATION OF SUBJECT MATTER

IPC⁶: C 07 D 213/65, 213/68, 295/108, 295/13, 409/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁶: C 07 D 213/00, 295/00, 409/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT; Chem. Abstr.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Questel: DARC, CAS; EPD: WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim N . |
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| A | Chemical Abstracts, Vol.110, No.4, 23 January 1989 (Columbus, Ohio, USA), page 499, column 1, abstract No.31325d, YOSHIMOTO, S. et al.: "Silver halide photographic material giving stable magenta color images", & Jpn. Kokai Tokkyo Koho JP 63,115,167 [88,115,167]. | 1-3 |
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☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

03 September 1997 (03.09.97)

Date of mailing of the international search report

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Information on patent family members

International application No.
PCT/KR 97/00128

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